EVALUATION OF AIR QUALITY AND HUMAN HEALTH SCIENTIFIC ISSUES INVOLVING PARTICULATE MATTER AND OZONE

(A Science Report to Governor John Engler)

Prepared by
Michigan Environmental Science Board
Air Quality Panel

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AUGUST 1997

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PREFACE

Michigan Environmental Science Board

The Michigan Environmental Science Board (MESB) was created by Governor John Engler by Executive Order 1992-19 on August 6, 1992. The MESB is charged with advising the Governor, the Natural Resources Commission, the Michigan Department of Natural Resources and other state agencies, as directed by the Governor, on matters affecting the protection and management of Michigan's environment and natural resources. The MESB consists of nine members and an executive director, appointed by the Governor, who have expertise in one or more of the following areas: engineering, ecological sciences, economics, chemistry, physics, biological sciences, human medicine, statistics, risk assessment, geology and other disciplines as necessary. Upon the request of the Governor to review a particular issue, a panel, consisting of MESB members with relevant expertise, is convened to evaluate and provide recommendations on the issue.

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EVALUATION OF AIR QUALITY AND HUMAN HEALTH
SCIENTIFIC ISSUES
INVOLVING PARTICULATE MATTER AND OZONE

MAJOR FINDINGS AND CONCLUSIONS

In November 1996, the U.S. Environmental Protection Agency's (USEPA) proposed new National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) and ozone. Controversy and debate (especially for PM) has surrounded this otherwise routine scientific review process. On June 25, 1997, President William Clinton approved slightly modified versions of the USEPA proposed NAAQSs. The new NAAQSs become effective 60 days following their publication in the *Federal Register.*

On November 21, 1996, the Michigan Environmental Science Board (MESB) was charged by Governor John Engler to evaluate the air quality and human health scientific assumptions, interpretations and conclusions regarding the impact of ground-level ozone and PM addressed in a May 1996 Natural Resources Defense Council (NRDC) report entitled, *Breath-Taking Premature Mortality Due to Particulate Air Pollution in 239 American Cities.* On December 4, 1996, the Governor's charge to the MESB was expanded to include a similar evaluation of the human health assumptions, interpretations and conclusions of the studies that served as the basis of the USEPA proposed air quality rules. Major findings and conclusions of the Panel are summarized below.

♦ The Panel identified eighty-three epidemiological studies published from 1967 through 1997 that examined the health effects of air pollution containing PM. Almost all of the studies found an association between measures of PM and heart- and lung-related dysfunction and death. An evaluation of the causal relationship between PM and health effects using standard epidemiological criteria indicated that the findings were consistent among studies and the intensity of adverse effects were related to the degree and time course of air pollution. It is reasonable to expect lung damage from inhalation of air pollutants but there is a lack of information regarding the mechanism by which PM damages the lung and causes death. Information from laboratory animals studies of PM toxicity and the paucity of information regarding a reduction of adverse health effects in the human population with a reduction of PM levels in the air provides a degree of uncertainty regarding whether or not PM is the causative agent for harmful effects from air pollution.

♦ A limited number of toxicology studies using laboratory animals have been conducted to understand the harmful effects of specific materials found as particles in air. Very few of these studies examined the effects of mixtures of particulates typically found in polluted urban air. The studies performed to date characterized the toxicity of specific materials, usually employed high doses and used methods of exposure that do not mimic human inhalation of air contaminants. The results of these studies indicate

that lung and heart function can be altered under the extreme conditions used in the experiments. However given the limited scope of the studies, the information derived from them cannot be used to provide support for the hypothesis that the levels of particulates commonly present in polluted air the U.S. are producing toxic effects in humans. The results of animal experiments in which exposures are more consistent with human exposures are needed to provide support for a cause and effect relationship between contaminated air and adverse effects on human health.

♦ Correlations between personal exposure to particulates and central (or regional) ambient air monitoring station measurements have not been adequately determined. The data that are available suggest a poor correlation may exist between these exposure parameters. Therefore, the use of routine central air monitoring data as a surrogate for personal exposure to particulates in inhaled air is subject to considerable uncertainty and can lead to potential bias and misclassification of exposure levels in the epidemiology studies completed to date.

♦ A comprehensive national network of monitors for $PM_{2.5}$ does not exist. Most studies have used a surrogate measure for these fine particles. While a good correlation between the levels in air of $PM_{2.5}$ and PM_{10} particles exists, the statistical relationship between health indicators and fine particles has been established primarily through use of surrogates measures. A direct measuring network for $PM_{2.5}$ is needed to provide information regarding the relationship between fine particles and adverse health effects.

♦ Members of the USEPA's 21-member Clean Air Scientific Advisory Committee were divided over the issue of causality between PM and mortality with some accepting: (1) a causal $PM_{2.5}$/mortality relationship, (2) a PM/mortality relationship but not a causal $PM_{2.5}$/mortality relationship., (3) PM as a surrogate for air pollution in general or some other component of air pollution as the causal agent, (4) a PM relationship caused by some unknown factor that is not necessarily related to air pollution and (5) a PM/mortality relationship that results from a statistical artifact.

♦ The MESB Air Panel concludes that there are significant, adverse human health effects associated with increases in environmental air pollution variables. Epidemiological studies have repeatedly shown statistically significant associations of air particulate matter levels with a variety of human health endpoints including increased hospitalizations and deaths from and heart and lung disease. Controversy currently remains regarding the nature and impact of confounding factors, the biological mechanism(s) which might be involved, the validity of exposure measures and, consequently, whether $PM_{2.5}$ causes the reported health effects. Additional epidemiological, toxicological and exposure matrices research are needed to resolve these controversies.

♦ A new eight-hour ozone NAAQS of 0.08 parts per million (ppm) concentration was approved on June 25, 1997. Compliance will be determined by averaging the fourth

highest eight-hour value each year for three consecutive years. The Panel acknowledges that the lower the standard the lower the exposure which should result in a lower biological response assuming, as current data suggest, there is no threshold concentration for ozone. The new standard was selected at the midpoint of the USEPA's proposed range of 0.07 ppm - 0.09 ppm with one to five allowable exceedences. Health risk estimates associated ozone concentrations within the proposed range as calculated by the USEPA indicated small differences which, because of uncertainties in exposure and dose-response relationships, could be considered as within the margin of error of the estimates. Therefore, selection of the new eight-hour standard of 0.08 ppm from among the proposed ranges of values appears to be a policy decision.

♦ The Panel further concludes that the air quality and adverse human health assumptions and predictions used by the NRDC in its report cannot be definitively determined to be valid or invalid given the current lack of conclusive epidemiological, toxicological, meteorological and human exposure data, and the resulting differences in scientific interpretation of existing data. The particular methodology used by the NRDC to develop its estimate is not unreasonable if used under an operating assumption that PM causes increased mortality and if correctly calculated. However, a majority of the Panel concludes that the value obtained by the NRDC for the number of premature deaths (64,000) attributed to PM in air cannot be considered reliable because of a recently recognized statistical error involved in its calculation and an uncertain causal relationship between $PM_{2.5}$ exposure and mortality.

♦ A minority statement regarding the public health significance of PM pollution and efficacy of the NRDC's methodology to estimate annual PM-associated premature deaths is presented.

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INTRODUCTION

Governor's Charge to the Michigan Environmental Science Board

The Michigan Environmental Science Board (MESB) was created by Executive Order 1992-19 on August 6, 1992. The MESB is charged with advising the Governor, the Natural Resources Commission, the Michigan Department of Natural Resources and other state agencies, as directed by the Governor, on matters affecting the protection and management of Michigan's environment and natural resources. The MESB consists of nine members and an executive director, appointed by the Governor, who have expertise in one or more of the following areas: engineering, ecological sciences, economics, chemistry, physics, biological sciences, human medicine, statistics, risk assessment, geology and other disciplines as necessary. Upon the request of the Governor to review a particular issue, a panel is convened to evaluate and provide recommendations on the issue.

On November 21, 1996, the MESB was charged by Governor John Engler (Engler, 1996a; see Appendix 1) to evaluate the air quality and human health scientific assumptions, interpretations and conclusions regarding the impact of ground-level ozone and particulate matter (PM) addressed in a May 1996, Natural Resources Defense Council (NRDC) report. On December 4, 1996, the Governor's charge to the MESB was expanded to include a similar evaluation of the human health assumptions, interpretations and conclusions of the studies that served as the basis of the U.S. Environmental Protection Agency's (USEPA) proposed air quality rules (Engler, 1996b; see Appendix 1). On January 21, 1997, an Air Quality Panel (Panel), composed of five MESB members and two guest scientists with expertise in toxicology, epidemiology, air quality, human medicine, and pathology, was convened to begin the investigation. The investigation consisted of the accumulation and evaluation of peer-reviewed and some non-peer-reviewed literature and data on the subject. In addition, verbal and written testimony was considered at five meetings (Harrison, 1997a; 1997b; 1997c; 1997d; 1997e). The report was prepared by the Panel with each individual assigned a specific topic or topics to address. The investigation lasted for a period of seven months.

The report addresses three directives from the Governor:

1. Thoroughly review the human health assumptions, interpretations and conclusions of the studies that serve as the basis of USEPA's proposed air quality rules,

2. Identify and evaluate the validity of the key air quality and human health assumptions contained in the NRDC report, and

3. Identify and evaluate the appropriateness of the methodology used to develop NRDC estimates of mortality and determine if there is sufficient evidence to attribute causality.

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DIRECTIVE 1. Thoroughly review the human health assumptions, interpretations and conclusions of the studies that serve as the basis of USEPA's proposed air quality rules.

Introduction

In November 1996, the USEPA proposed new National Ambient Air Quality Standards (NAAQS) for PM and ozone (USEPA, 1996a; 1996b; 1996e; 1996f). Controversy and debate (especially for PM) has surrounded the scientific review process with several researchers, environmentally-oriented and health-oriented organizations professing that the scientific data more than justify the more restrictive standards and that such standards are necessary in order to avoid a premature loss of a large number of lives annually (American Lung Association, 1997; Browner, 1997; Lippmann, 1997; Nichols, 1997; Samet *et al*., 1997; Schwartz, 1997; Shy, 1997; Thurston, 1997; American Lung Association of Michigan, 1996; Shprentz, Bryner and Shprentz, 1996; Lippmann *et al*., 1996; NRDC, 1996b; Wilson and Spengler, 1996; Samet, Zeger and Berhane, 1995; Cotton, 1993). On the other hand, some researchers, states and industrial groups have expressed concern with the use of speculative and inconclusive scientific data on which to base the new standards and/or the potential high cost associated with implementation of the proposed standards (Engler, 1997; Fialka, 1997; Harding, 1997a; 1997b; 1997c; Hartsock, 1997; Huebner and Chilton, 1997; Jones, 1997; Keating; 1997; Brown, 1996; Moolgavkar and Luebeck, 1996; Sierra Research, Inc., 1996; Wolff, 1996a; 1996b; 1996c; Lipfert and Wyzga, 1995a). The level of debate became even more evident with pro and con discussions reaching the halls of Congress (Dingell *et al*., 1997; John *et al*., 1997) and eventually resulting in the direct intervention by the President of the United States. On June 25, 1997, President William Clinton approved slightly modified versions of the USEPA proposed NAAQSs for PM and ozone (USEPA, 1997). The new NAAQSs become effective 60 days following their scheduled July 19, 1997 publication in the *Federal Register*.

It should be understood that the MESB is neither a state policy body nor an advocate for or against any particular environmental or public health cause. Consequently, the role of the MESB Air Panel in addressing this Directive is not to endorse or refute the approved USEPA NAAQSs but rather to provide an objective evaluation of the current multi-disciplinary scientific and technical information, which serves as the basis for them. In the case of the role of PM- and ozone-related air pollution in human morbidity and mortality, the existing scientific data do not allow for a straightforward interpretation and controversy exists regarding the validity of health risk estimations drawn from it. A diversity of scientific opinion exists in the USEPA's external advisory committee convened to address the subject and in other scientific groups meeting to evaluate the data. Within the MESB Panel appointed to address the issue, there has also been diversity of opinion and this report will undoubtedly be seen by some readers to reflect an imperfect consensus.

Proposed Air Quality Standards

Under the 1967 Clean Air Act, the Health, Education and Welfare Department was directed to prepare criteria documents summarizing the science on ubiquitous air pollutants. The 1970 Clean Air Act Amendments required the USEPA to set the NAAQSs for these ubiquitous pollutants. In 1971, the USEPA set NAAQSs for sulfur dioxide, carbon monoxide, nitrogen dioxide, photochemical oxidants (which later was changed to ozone), and PM. As a result of the 1977 Clean Air Act Amendments, the USEPA Clean Air Scientific Advisory Committee (CASAC) was created and charged with evaluating the scientific basis for the NAAQSs every five years (USEPA, 1996a; 1996b). Reviews have been conducted by CASAC as new scientific information has become available (Wolff, 1997).

The original PM standard was set for total suspended particulates (TSP), which included particles with diameters less than about 40 micrometers (µm) (PM_{40}) at 260 micrograms per cubic meter (µg/m^3) for a 24-hour period and 75 µg/m^3 for an annual average (USEPA, 1996b). Subsequently, it was shown that PM greater than 10 µm was not inhaled so in 1987 the standards were changed to PM_{10} and set at 150 µg/m^3 for 24 hours and at 50 µg/m^3 for an annual average. It was later realized that mouth breathing people took in PM_{10} particles but nose breathers only inhaled particles less than 2.5 µm (Wolff, 1996a).

The most recent USEPA PM review was ordered by the court as a result of a legal suit brought against the agency by the American Lung Association (USEPA, 1996b). The USEPA Administrator was given until July 19, 1997 to complete the review and make a decision. In June 1996, the USEPA CASAC affirmed the 24-hour and annual average PM_{10} standards and recommended that a standard for fine PM less than or equal to 2.5 µm ($PM_{2.5}$) be established (Wolff, 1996a). However, it could not reach a consensus on the level, averaging time or form for the $PM_{2.5}$ standard (Wolff, 1996a). The USEPA proposed that the NAAQS retain the existing annual and 24-hour standards for PM_{10} and establish a new annual and 24-hour standard for $PM_{2.5}$ of 15 µg/m^3 and 50 µg/m^3, respectively (USEPA, 1996b; 1996f). The final PM standards, as approved by President Clinton on June 25, 1997, modified the USEPA proposal by changing the proposed 24-hour standard for $PM_{2.5}$ to 65 µg/m^3. Five years will be allowed for constructing and deploying monitors capable of detecting $PM_{2.5}$ and states will be afforded an additional three years to develop implementation plans. The USEPA will have one and one half years beyond that to review and approve the state plans (USEPA, 1997).

In terms of ozone, the primary standard was established in 1971 at a one-hour ozone concentration of 0.08 parts per million (ppm). The standard was changed in 1977 and later affirmed in 1993 to a one-hour ozone concentration of 0.12 ppm with three allowable exceedences in three years (USEPA, 1996a; 1996h). In 1996, the USEPA proposed a three-year average of the third highest eight-hour average for each year. This number cannot exceed 0.08 ppm (USEPA, 1996h). The CASAC concurred with the USEPA that (1) ozone was the logical surrogate for controlling photochemical oxidants, (2) the proposed eight-hour standard was more appropriate as a human

health-based standard than the current one-hour standard, and (3) the form of the eight-hour standard be more robust than the present one-hour standard (Wolff, 1995). The CASAC expressed concern, however, that none of the possible standards, from among the range of eight-hour concentrations of 0.07 ppm to 0.09 ppm with one to five allowable exceedences, was necessarily more protective of public health than another (Wolff, 1995). On June 25, 1997, President Clinton modified the USEPA proposal by approving an 0.08 ppm ozone concentration with compliance to be determined by averaging the fourth highest eight-hour value each year for three consecutive years (USEPA, 1997).

Discussion

Particulate Matter

Human Health Assumptions - The USEPA presented its human health assumptions, interpretations and conclusions for its proposed air quality standards in its PM Criteria document (USEPA, 1996b) and Staff paper (USEPA, 1996i). Table 1 presents a summary of these issues for PM. Central to the discussion of the various assumptions and conclusions used to develop the proposed PM NAAQS is the question of causal relationship between PM exposure and human health effect. Presented below is an overview of the critical information available which addresses these issues from the various scientific and technical perspectives.

Epidemiological Perspective – Forty-five epidemiological studies (42 ecologic and 3 cohort) addressing the relationship between mortality and air pollution were identified and reviewed (see Appendix 2, Tables 1, 2 and 3). These studies were identified by performing a Medline (Inteli-Health Inc., 1997) literature search and reviewing the references cited in review articles and USEPA documents. Forty-two of the studies examined changes in mortality over time. Three of the studies (Pope *et al*., 1995; Dockery *et al.* 1993; Abbey *et al*., 1991) looked at differences in mortality between different locations. Standard epidemiological criteria (Lilienfield and Lilienfield, 1980) were used in this review to determine the likelihood of a causal relationship between particulate air pollution, particularly particles less than 2.5 μm, and mortality. The criteria used were:

1. Biological Plausibility,
2. Consistency of Results Across Studies.
3. Dose-Response,
4. Intervention,
5. Specificity,
6. Strength of Association, and
7. Temporality.

Biological Plausibility - An aspect of biological plausibility evaluation consists of data from human epidemiology indicating that there is a reasonable and observable association between extent and type of tissue injury and subsequent death. The large number of morbidity studies showing effects on the cardiorespiratory system when considered with the large number of mortality studies, and the fact that injury and death

are both associated with the same organ systems and PM air pollution, including $PM_{2.5}$, indicate that biological plausibility criteria are at least partially satisfied based on data from humans. The biological effect of particulates includes lung inflammation and epithelial injury. Thirty-eight morbidity studies conducted by multiple investigators in multiple geographic locales have shown an increase in emergency room visits, and hospitalizations as well as a decrease in pulmonary function with increasing doses of particulates (Appendix 2, Table 4). Most of these studies used TSP or PM_{10} as the measure of particulate pollution. Five of these studies (Delfino *et al.*, 1997; Peters *et al.*, 1997; Romieu *et al.*, 1996; Koenig *et al.*, 1993; Abbey *et al.*, 1991) used $PM_{2.5}$ as the measure of particulate pollution and found an association with different measures of respiratory morbidity and $PM_{2.5}$.

Table 1. Key USEPA PM/health-related assumptions, interpretations and conclusions.[(a)]

1. Many epidemiological studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints.
2. Associations of both short-term and long-term PM exposure with most of the health endpoints have been consistently observed.
3. Uncertainty remains regarding the shapes of PM exposure-response relationships, the magnitude and variability of risk estimates, the time intervals over which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations and the nature and magnitude of the overall public health risk imposed by PM exposure.
4. The underlying biologic mechanisms for PM have not yet emerged.
5. Individuals with cardiovascular or pulmonary disease, especially if they are elderly, are more likely to suffer severe health effects (mortality or hospitalization) related to PM exposure than are healthy young adults.
6. Children, asthmatics and smokers are at increased risk for ambient PM exposure effects.
7. Indices of PM exposure that have been most consistently associated with health endpoints are by PM_{10} and PM_{15} and fine particle indicators. Less consistent relationships have been observed for TSP and the coarse fractions of $PM_{10-2.5}$.
8. Central site measurements of fine particle indicators can be useful in PM epidemiology studies.
9. In view of geographic differences in ambient PM mixtures and demographics, broad generalization and application of some single best estimate of relative risk for a given increment in concentration of a given particle indicator (e.g., PM_{10}, $PM_{2.5}$, etc.) would be subject to much uncertainty.

(a) From USEPA, 1996b; 1996i.

Biological plausibility based on results from studies of biological mechanism in laboratory-based experiments will be presented in the Toxicological Perspective section of this report. There are insufficient animal laboratory experimental studies completed at this time to make a judgment about the biological plausibility of the mortality findings. However, the consistent results of increased human cardiorespiratory morbidity for particulate pollution, including the five studies using $PM_{2.5}$ as the measure of exposure, are suggestive evidence of biological plausibility. If the morbidity studies did not support the results of the mortality studies, the clinical relevance of the mortality studies

would come under question. Modeling work using the effect of particulates on lung function show that quite small absolute impacts of air pollution on lung function could be responsible for the mortality observed in the cross-section studies (Wilson and Spengler, 1996). The criteria for biological plausibility for increased mortality are partially met given the large number of morbidity studies showing an association between PM air pollution, including $PM_{2.5}$, and consistent effects on cardiorespiratory morbidity.

Consistency of Results Across Studies - Of the 45 studies identified, all but six of the studies reviewed (see Appendix 2, Table 3) found an increase in mortality with increased particulate pollution. Measures of particulate pollution usually were in the form of TSP or PM_{10}. Only two studies (Pope *et al.*, 1995; Dockery *et al.*, 1993) used $PM_{2.5}$ as the measure of pollution. Both of these studies showed an association between mortality and $PM_{2.5}$. Many different investigators have conducted these mortality studies in a variety of geographic locations (Appendix 2, Tables 1, 2 and 3). The criteria for consistency are met for particulate pollution; however, limited data are available on $PM_{2.5}$.

Dose Response - There are several issues related to dose:

1. Individual Versus Community Exposure. People spend 85 percent of their time indoors (USEPA, 1996c; 1989) and there is concern that the outdoor measurements of particulates used in the mortality studies do not accurately reflect individual exposure. If this were the case, the association of adverse health effects with exposure to PM_{10} and $PM_{2.5}$ may be an artifact of inaccurate exposure assessment.

2. $PM_{2.5}$ vs. PM_{10}. There are two mortality studies that used $PM_{2.5}$ as the particulate exposure measurement (Pope *et al.*, 1995; Dockery *et al.*, 1993). However, these are the two methodologically strongest mortality studies. There are five morbidity studies that used $PM_{2.5}$ for the particulate exposure measurement (Delfino *et al.*, 1997; Peters *et al.*, 1997; Romieu *et al.*, 1996; Koenig *et al.*, 1993; Abbey *et al.*, 1991). $PM_{2.5}$ accounts for approximately 60 percent of PM_{10} and, generally, there is a good correlation between the two values (Pope *et al*., 1995; Iverson, 1995; Bahadori *et al*., 1995; Burton, Suh and Koutrakis, 1996; Dockery and Pope, 1994; Spengler and Thurston, 1983). Consequently, from consideration of the results of human epidemiology studies, PM_{10} should be a useful surrogate of $PM_{2.5}$ exposure in the large number of studies that used PM_{10} as the measure of exposure.

3. Different Statistical Models Used Different Exposure Measures. A variety of different statistical approaches and models have been used to conduct the mortality studies (Appendix 2, Tables 1, 2 and 3). Cox proportional hazard regression models were used for the cohort epidemiological studies. Poisson, linear and multiple regressions were used for the time series analyses. Positive results are not specific to a particular statistical model.

4. Adequate Control of Confounders. Community-wide confounders, such as weather or influenza outbreaks or individual confounders such as cigarette smoking or exercise levels have been suggested as possible reasons for the association between particulate pollution and mortality. Community-wide confounders could be important in the ecologic time-series type studies. All the studies reviewed controlled for confounders (Appendix 2, Tables 1, 2 and 3). Personal life-style habits, including cigarette smoking, occupational exposure, educational level, body mass, alcohol use, diabetes and hypertension, were controlled for in the cohort studies (Pope *et al.*, 1995; Dockery *et al.*, 1993; Appendix 2, Table 1). The two cohort studies have been criticized for not controlling for physical activity level (Lipfert, 1995). Given that the studies controlled for education level and body mass, other personal life style factors such as exercise or diet which are closely associated with education level and body mass are less likely to have an independent effect. Also, there is no association between physical activity level and the risk of death from respiratory disease that is associated with particulate pollution in a number of the studies (Ostro, *et al*., 1997; Vigotti *et al*., 1996; Ostro *et al*., 1995; Xu *et al*., 1994; Pope, Schwartz and Ransom, 1992; Schwartz and Dockery, 1992a; Kinney and Özkaynak, 1991; Archer, 1990).

Since the mortality rates in the more highly polluted cities remain elevated over the less polluted cities, the effect is not solely an increase in deaths on days of increased pollution of individuals who would have died shortly anyway. Although neither cohort study directly controlled for underlying heart disease, the studies controlled for the risk factors of heart disease.

5. Dose-Response Trend. The different studies reviewed show an approximately one percent increase in overall mortality, 3.4 percent increase in respiratory mortality and 1.4 percent increase in cardiovascular mortality for each 10 $\mu g/m^3$ increase in particulate air pollution (Dockery *et al*., 1994). Table 2 summarizes the estimated health endpoint effect per 10 $\mu g/m^3$ increase in PM_{10}.

6. No Effect Threshold Level. The determination of a threshold is not only a biological factor but also a factor of sample size and it would be very difficult to determine a no-effect level (Dockery and Pope, 1994). The lowest level of $PM_{2.5}$ for which the two prospective cohort studies examined mortality was 10 $\mu g/m^3$. The effect was linear above that level.

Considering all of the issues presented above, it appears that the criteria for dose-response are met.

Intervention - There were no mortality studies conducted after implementation of clean up of the air. The intermittent closing of a steel mill which was the major source of particulate pollution in Utah Valley, Utah was associated with a decrease in respiratory hospital admissions (Pope, Schwartz and Ransom, 1992). Generally, intervention studies are not available until after acceptance of the causal association and control measures are implemented. The criteria for intervention were not met.

Specificity – Many of the mortality studies reviewed (see Appendix 2, Tables 1 and 2) show increased risk for overall mortality. When specific cause of death is examined, there is increased mortality for cardiopulmonary disease and not for conditions which should not be associated with particulate pollution such as accidents. Specific and limited causes of mortality are associated with particulate pollution. The criteria for specificity are met for particulate pollution.

Table 2. Approximate range of estimated effects measured as percent change in health endpoint per 10 µg/m^3 increase in PM_{10} for the different basic study designs.[(a)]

Health Endpoints	Acute Exposure		Chronic Exposure	
	Population-Based	Cohort-Based	Population-Based	Cohort- or Sample-Based
Mortality	Total: 0.5-1.5 Resp: 1.5-4.0 Cardio:0.5-2.0	--	Total: 0-5	Total: 3-9 Cardiopulmonary: 5-9 Lung Cancer: 0-9
Respiratory Health Care	Hosp. Admit: 0.5-4.0	--	--	--
	Emergency Visits: 0.5-3.5	--	--	--
Decrease in Lung Function	--	FEV: 0.05-0.35 PEF: 0.04-0.25	--	Lung function: 0-2
Respiratory Symptoms, Disease	--	Lower: 0-15 Upper: 0-7 Cough: 0-25 Asthmatic attacks: 1-12	--	Emphysema, Chronic bronchitis or cough: 10-25
Restricted Activity	Grade school absences: 1.0-4.0	Restricted activity days: 1.0-5.0	--	--

(a) From Wilson and Spengler, 1996.

Strength of Association - The magnitude of the risk across the studies showed relative risks less than 1.5 (50% increase). At these relatively low risks there is a concern that uncontrolled factors and not particulate pollution may be the cause of the increase risk. These relative risks were, however, statistically significant. When common adverse outcomes such as cardiovascular disease are studied, risk ratios are typically lower than for rarer outcomes such as cancer. For example, while the risk of lung cancer among cigarette smokers has been shown to be greater than eight-fold, the risk of heart disease among cigarette smokers is less than two (Hennekens and Buring, 1994). The criteria for strength of association are not met for particulate pollution.

Temporality - Associations between mortality and particulate pollution are shown when particulate levels for the same day up to nine days before death are used (see Appendix 2, Tables 1 and 2). The criteria for temporality are met for particulate pollution.

Summary - Eighty-three studies published from 1967 through 1997 were identified that examined the health effects of particulates. Almost all the studies found an association

between measures of particulate pollution and cardiopulmonary morbidity and mortality. Evaluation criteria for a causal relationship between particulate pollution and morbidity/mortality in humans are met for consistency of results, dose response, specificity and temporality, and partially met for biological plausibility. The criteria for intervention and strength of association were not met.

Toxicological Perspective - Toxicological evidence for ambient particle-induced lung injury is needed to strengthen biologic plausibility for the epidemiological correlations between exposure to increased ambient concentrations of airborne particulates (PM_{10} and $PM_{2.5}$) and respiratory morbidity and mortality. Only through well-designed toxicological studies will it be possible to identify biologic mechanisms that could explain the epidemiological observations.

PM is a broad term that encompasses thousands of chemical species, many of which have not been investigated in controlled laboratory or human studies. A complete review of all the types of PM that have been studied are presented elsewhere (USEPA, 1996b). The purpose of this portion of the report is to review recent toxicological studies that: (1) may elucidate health effects of major constituents of PM (e.g., sulfates, diesel exhaust, transition metals) and/or (2) contribute to enhanced understanding of the epidemiological studies (e.g., real world particles collected from urban atmospheres, surrogate particles).

The biological responses to inhaled particles are dependent on the physical and chemical characteristics of the PM, the total exposure, and the health status of the host. Toxicological studies have examined the effects of exposure to: (1) a single type of PM with a specific chemical and physical makeup; (2) a mixture of PM of different composition or (3) a combination of PM and gases (Bascom *et al*., 1996; USEPA, 1996b). The adverse effects from exposure to complex pollutant mixtures are important because people are not exposed to a single ambient air pollutant. However, controlled exposure studies of humans or animals rarely involve more than two pollutants simultaneously or sequentially. The exception to this are the studies on diesel and gasoline engine emissions, where the exposure has been to the specific mixture (USEPA, 1996b). In studies involving more complex mixtures (e.g., urban ambient air) it is difficult, if not impossible, to assess the relative contributions of individual specific components.

The chemical composition and physical characteristics of the full range of ambient airborne particles in outdoor air have not been fully determined and it is improbable that the heterogeneous nature of outdoor air particles can be fully duplicated in controlled human or animal studies in the laboratory. PM in the atmosphere is composed of organic and inorganic materials, whose relative composition can vary significantly, depending on the point sources from which the particles are generated. Many health effects of particle air pollution are thought to reflect the combined toxicity of several agents (e.g., carbon, sulfates and metals) within the complex air mixture (Costa and Amdur, 1996). Recent epidemiological studies, however, suggest that the health effects of PM at current ambient concentrations (near NAAQSs) may be less affected by gross particle composition and nominal particle size (<10 µm) than by gravimetric

estimates of ambient exposure (Costa and Amdur, 1996). However, so little is understood about the these epidemiological findings that it is still possible that the relatively crude (PM_{10}) mass-based correlation with the biologic effects may be only a surrogate for the actual toxicant. Unfortunately, there are not yet enough data from toxicology studies regarding this issue.

Approaches to the study of particles have ranged from *in vivo* and *in vitro* screening tests to standardized bioassays such as those used by the National Toxicology Program (Bascom *et al*., 1996). The difficulties encountered in assessing responses to particulate pollutants include uncertainties related to particle size, deposition sites, and changes in aerosol composition during particle generation. Intratracheal instillation of particles, suspended in aqueous solutions, into the lungs of laboratory animals can be a convenient way of comparing acute toxicity among different particle samples, but it may not produce the same biologic responses that would be generated by inhalation exposure. The intrapulmonary sites of particle deposition in laboratory animal experiments will vary depending on the method of particle exposure (Brain *et al*., 1976). Inhalation exposure is a more environmental and physiologically relevant method of exposure for assessing the toxicity of airborne pollutants than is intratracheal instillation.

Most PM studies considered in laboratory animal toxicology and occupational studies utilize particles in the 0.1 µm to 10 µm (mean aerodynamic diameter) size range (USEPA, 1996b). However, the enormous numbers and huge surface areas of the ultrafine particles demonstrate the importance of considering size of the particle. Ultrafine particles with a diameter of 20 nanometers (nm) when inhaled at the same mass concentration have approximately six orders of magnitude higher number concentration than a 2.5 µm diameter particle, and particle surface area is also markedly increased (Oberdorster *et al*., 1995).

Most of the laboratory animal studies summarized here used high PM concentrations, relative to those in ambient air, even when laboratory animal-to-human dosimetric differences are considered. This raises a question about the relevance of, for example, a rat study at 5,000 $\mu g/m^3$ in terms of direct extrapolation to humans who are exposed to low ambient concentrations of air pollutants.

In spite of these difficulties, results from laboratory animal studies provide certain toxicological principals for PM. The large literature database clearly shows that the site of respiratory tract deposition of PM influences the health outcome. The most important characteristic influencing the deposition of a particle in the respiratory tract is size (Moss and Cheng, 1989). Particle size is often expressed in terms of aerodynamic diameter, defined as the diameter of unit density sphere that has the same settling velocity as the particle in question. Models of inhaled particle deposition relate aerodynamic particle diameter to the site of deposition in the respiratory tract. Most inhaled particles greater than five µm in aerodynamic diameter, such as road dust, deposit in the upper airways or larger tracheobronchial airways. Smaller particles are more likely to deposit in the periphery of the lungs. The sites of particle deposition also are influenced by hygroscopic growth of particles in the airways, the shape and

dimensions of the airways, ventilatory patterns, oral versus nasal breathing, and respiratory secretions (e.g., mucus).

The residence time of the PM in the respiratory tract may also be a critical factor in how the host responds to this inhaled material. Particles are cleared from the respiratory tract by several mechanisms. Those deposited in the anterior nasal airways are expelled by sneezing or wiping, while the remainder of particles deposited in the nose is cleared to the pharynx and subsequently swallowed. Particles deposited in the tracheobronchial airways (e.g., trachea, bronchi and bronchioles) are cleared proximally by the mucocilliary apparatus to the oral pharynx and swallowed. Particles deposited in the distal terminal and respiratory bronchioles, alveolar ducts or alveoli are cleared by phagocytizing macrophages and/or dissolution. A small fraction of these deposited particles will migrate through the alveolar tissue directly into the lung lymphatic system.

In addition to PM size and deposition and clearance properties, toxicity of PM is also dependent on its chemical composition. Brief summaries of the known toxicology of specific PMs (with specific chemical and physical characteristics), that may be present in the ambient air and are of concern for human health are subsequently addressed.

Acid Aerosols - The bulk of laboratory animal toxicological database on PM involves sulfur oxide particles, primarily H_2SO_4 (USEPA 1996b). The observed responses to these acid aerosols are likely due to H+ rather than to $SO_4^=$ (National Research Council, 1978). Acidic sulfates exert their action throughout the respiratory tract, with the response and location of effect dependent upon particle size and mass and number concentration. At very high concentrations that are not environmentally realistic, mortality will occur following acute exposure due to laryngospasm or bronchoconstriction. Both acute and chronic exposure to H_2SO_4 at levels well below lethal levels will produce functional changes in the respiratory tract. These changes are largely due to bronchoconstrictive action (USEPA, 1996b). The lowest effective level of H_2SO_4 producing a small transient change in airway resistance in the guinea pig after inhalation is a one hour exposure to 200 $\mu g/m^3$ (Chen *et al*., 1992). In general, the smaller size droplets (submicron) are more effective in altering pulmonary function.

Severe morphologic alterations in the respiratory tract will occur at high concentrations (>1,000 $\mu g/m^3$) of particles in the size range of 0.3 µm to 0.6 µm (USEPA, 1996b). At low concentrations (>100 $\mu g/m^3$) of comparable particle size and with chronic exposure, the main response is hypertrophy and hyperplasia of mucous secretory cells in the airway epithelium. This alteration is a feature often observed in chronic airway diseases (chronic bronchitis, asthma) in humans.

Pulmonary defense mechanisms are also altered by exposure to H_2SO_4 at levels less than 1,000 $\mu g/m^3$ (USEPA, 1996b). Alterations have been demonstrated in host defenses such as resistance to bacterial infection and the bronchial mucociliary clearance.

Metals - Data from occupational studies and laboratory animal studies indicate that acute inhalation exposures to high levels or chronic exposures to low levels (although

high compared to ambient levels) of metal PM compounds (e.g., iron oxides, cadmium and chloride) can have toxic effects on the respiratory tract (USEPA, 1996b). However, it is doubtful that the metals at concentrations present in the ambient atmosphere (1 $\mu g/m^3$ to 14 $\mu g/m^3$) could have significant acute effects in healthy individuals. A few studies examining the potential for transition metals to cause lung injury by the generation of oxidant free radicals have been conducted *in vitro* and in animals by instillation (Costa *et al*., 1994a; 1994b; Aust, 1989; Minotti and Aust, 1987). The results of studies examining the toxic potential of transition metals from urban collected PM_{10} are presented later.

Ultrafine Aerosols - There are only limited data available from human studies or laboratory animal studies on ultrafine aerosols (USEPA, 1996b). The ultrafine particle phase has a median diameter of approximately 20 nm. They are present in the ambient air as single particles and represent an extremely small portion of the mass (USEPA, 1996b). However, ultrafine particles are present in high numbers and have a high collective surface area. There are *in vitro* studies that show that ultrafine particles have the capacity to cause injury to cells of the respiratory tract (Oberdorster *et al*., 1994; 1992). High levels of ultrafine particles, as metal or polymer "fumes", are associated with toxic respiratory responses in humans and other mammals (Alarie and Anderson, 1981; Waritz and Kwon, 1968). Insufficient information, however, is available at the present time to determine whether ambient ultrafine particles may play a critical role in PM-induced mortality.

Diesel Exhaust - The biologic effects of acute and chronic exposures of laboratory animals to diesel exhaust have also been examined. Acute toxic effects caused by exposure to diesel exhaust are mainly attributable to the gaseous components (i.e., mortality from carbon monoxide intoxication and lung injury from respiratory irritants). When the exhaust is diluted to limit the concentrations of these gases, acute effects are not seen (USEPA, 1996b).

Chronic inhalation exposures (>1 year) of rodents to diesel exhaust cause marked pathologic alterations in the bronchoalveolar regions of the lungs with impairment of PM clearance (Mauderly *et al*., 1994). These long-term exposures can result in lung inflammatory, fibrotic, and emphysematous lesions. These pathologic effects after chronic exposure are considered to be due to the particle rather than the gas phase, since the long-term effects seen with complete diesel are not found or are found at much lesser extent in animals when diesel exhaust is filtered to remove the particles (USEPA, 1996b). Chronic studies in rodents have demonstrated pulmonary effects at 200 $\mu g/m^3$ to 700 $\mu g/m^3$. A range of no adverse effect levels has been estimated from 200 $\mu g/m^3$ to 400 $\mu g/m^3$ (USEPA, 1996b).

Bioaerosols - Ambient bioaerosols include fungal spores, pollen, bacteria, endotoxin, viruses, and plant and animal debris. This inhaled PM can produce health problems that include infections, hypersensitivity reactions, and toxicoses. However, it is improbable that bioaerosols, at the concentrations present in the ambient environment, could account for the observed effects of PM on human mortality and morbidity reported in PM epidemiological studies. Bioaerosols generally represent a small

fraction of the measured urban ambient PM mass and are typically present at lower concentrations during the winter months when notable ambient PM effects have been demonstrated (USEPA 1996b). Bioaerosols also tend to be in the coarse fraction of PM (>10 µm) which is thought to be less of a toxic hazard compared to smaller particles. Therefore, bioaerosols are not thought to play a significant role in PM-related effects on mortality and morbidity observed in recent epidemiological studies.

Urban Atmospheres or Emission Sources Toxicological Studies of PM_{10} - Though epidemiological evidence supports the association between ambient PM_{10} particles and increased incidences of morbidity and mortality related to cardiopulmonary diseases, the causal agent(s) or the biologic mechanism(s) responsible for these adverse effects have not been identified. As was mentioned above, toxicological studies have demonstrated that numerous individual PM species (e.g., acid aerosols, diesel exhaust, metals and ultrafine particles), that may be present in the ambient air, can individually cause a wide spectrum of adverse pulmonary responses (e.g., bronchoconstriction, pulmonary inflammation, airway epithelial cell injury). However, most of the reported adverse effects in *in vivo* animal studies or in *in vitro* cell culture studies are induced at extremely high concentrations, relative to ambient concentrations. People are exposed daily to low concentrations of a complex mixture of air pollutants (e.g., particles - inorganic and organic and gaseous agents - ozone and SO_2). In addition, many of the animal studies of urban PM_{10} have used intratracheal instillation to deliver particles to the lungs, rather than inhalation, a more physiologic method of PM delivery to the respiratory tract. The route of particle delivery to the lungs of laboratory animals can have a significant effect on the deposition and clearance of the particle and the host's subsequent response to the PM (Henderson *et al*., 1995; Brain *et al*., 1976).

Ideally, toxicological information used for estimating the risk to human health and for setting national air quality standards must include data from inhalation toxicological studies that use near ambient exposure conditions. Though several toxicology studies are currently underway to study the health effects of ambient concentrations of PM with a mean aerodynamic diameter of less than 10 µm (PM_{10}) collected from an urban air source, no such reports have been published yet in peer-reviewed scientific journals. Therefore, there are insufficient laboratory animal data at the present time to support a toxic effect(s) or likely mechanism(s) that would explain the development of adverse effects of PM_{10} or $PM_{2.5}$ at the low airborne mass concentrations observed in the urban environment. Recently published or soon to be published toxicological studies relevant to this issue are presented below.

Investigators have suggested that the health effects of PM_{10} may be due to the induction of injurious levels of oxidant free radicals that cause pulmonary inflammation and epithelial injury. Li *et al*. (1996) have demonstrated that intratracheal instillation of rats with PM_{10} particles collected from an urban monitoring station does cause lung inflammation along with increased epithelial permeability indicating alveolar cell injury. Their hypothesis that the lung epithelial injury was due to oxidative properties of PM_{10} is supported by previous observations that PM_{10} particles produce plasmid DNA scission *in vitro*, a sensitive assay for detecting the ability of particles to cause oxidant free

radical injury (Gilmour *et al*., 1996). The free radical-induced injury may have been due to hydroxyl radicals since it was substantially inhibited by mannitol, a free-radical scavenger.

Many kinds of particles which are known to induce lung injury have variable amounts of free radical activity at their surfaces (e.g., asbestos and quartz) (Witschi and Last, 1996). Furthermore, the role of iron or other transition metals found in airborne particles in producing highly injurious oxidant free radicals has been suggested as a unifying theme in particle toxicity (USEPA, 1996b). The results of recent animal studies by Costa and Dreher (In press) have also supported the hypothesis that the PM-associated transition metals (e.g., iron, nickel, and vanadium) are the primary determinants of the acute inflammatory response in the lungs of rats intratracheally instilled with PM collected from combustion emission sources or ambient environments. The presence of soluble transition metals on residual oil fly ash (ROFA) particles, an airborne combustion by-product emitted from facilities that burn residual oil, are consistent with the anthropogenic process where volatized metal, sulfuric acid vapor, and SO_2 condense on submicron ash particles, forming the complex acid aerosol mixture (Linak and Wendt, 1994).

These and other investigators speculate that these transition metals induce an unusually high oxidative burden due to their ability to participate in reduction/oxidative cycling. This oxidative burden may lead to the activation of transcriptional factors and subsequent expression of genes encoding proinflammatory mediators (e.g., cytokines) that results in pulmonary inflammation and alveolar cell injury. They also contend that there are a number of reasons why transition metals may be plausible agents to explain the recent ambient air PM epidemiological findings. For example, these metals are found in highest concentration in urban air PM when compared to that of rural and remote locations (Schroeder *et al*., 1987). Their findings are consistent with the results of Pritchard *et al*. (1996), who also demonstrated a correlation between urban ambient air PM-associated metal content and acute lung injury in animals. In addition, their findings are consistent with studies demonstrating that exacerbation of some respiratory symptoms in humans is associated with PM_{10} content (Dusseldorp *et al*., 1995).

Because the epidemiological data of PM-associated mortality also suggest that people with cardiopulmonary diseases are most at risk for PM-induced deaths, a few toxicology studies have been conducted using animal models of cardiopulmonary disease to try to elucidate the etiology of the apparent susceptibility of this subpopulation to PM exposure. Costa and Dreher (In press) used an animal model of pulmonary hypertension to study the effects of ROFA particles on the compromised animal. Pulmonary vasculitis/hypertension was induced in male rats using an intraperitoneal injection of the pulmonary toxin monocrotaline (MCT). MCT-treated rats were sensitive to the intratracheal instillation of the fly ash particles with a significant increase in mortality compared to groups of rats treated with MCT or ROFA alone. The cause of death in the MCT-ROFA animals appeared to be related to altered cardiac function, although it was not clear whether death was associated with direct cardiac injury or whether it was secondary to pulmonary failure. These investigators have not yet studied the effects of inhaled concentrations of ambient PM on MCT-treated rats.

However, Godleski *et al*. (1996), have reported in a recent abstract, significant mortality (19%) in MCT-treated rats with inhalation of concentrated ambient Boston air (approximately 350 Urban Atmospheres or Emission Sources, 6 hours/day, 3 days). These investigators also reported significant mortality (37%) in rats with SO_2-induced chronic bronchitis after exposure to the same concentration of this urban PM. No mortality was observed in PM-exposed rats without pre-existing disease.

Although these initial results from toxicological studies using laboratory animals demonstrate that high concentrations of PM_{10} can induce marked pulmonary injury in healthy and compromised rats, there are presently no toxicological data that indicate that ambient concentrations of urban PM_{10} or $PM_{2.5}$ will or will not cause adverse effects on the respiratory tract in laboratory animals. In addition, published toxicological studies have been restricted to those in which the PM was administered to the lungs by intratracheal instillation rather than by the more environmentally and physiologically relevant method of inhalation exposure. Well-designed inhalation studies of ambient concentrations of urban PM are lacking in the scientific literature. There are at the present time insufficient toxicological data to lend support or to negate the findings of epidemiological studies that increases in ambient levels of PM_{10} or $PM_{2.5}$ can cause increases in morbidity and mortality in the human population.

Human Exposure Issues - The USEPA regulatory authority for PM pertains only to the ambient air, defined in 40 CFR 50.1(e) as *"... that portion of the atmosphere, external to buildings, to which the general public has access* ..." (USEPA, 1994). People spend approximately 85 percent of their time indoors (USEPA, 1996c; 1989), but outdoor PM can penetrate to indoors and constitute a major fraction of the indoor air composition (USEPA, 1996b). When people are indoors, they are exposed to a mixture of ambient PM and particles generated indoors from non-regulated sources, such as PM from cigarette smoke, cooking, heating and personal activities such as vacuuming.

Personal exposure may act as a confounder in epidemiological studies that use an inferred community exposure to ambient PM as a parameter to correlate with community health parameters. An individual's personal exposure to total PM is the critical parameter for analysis if that person is a member of a cohort whose health outcomes are being tracked individually, and cause and effect conclusions drawn therefrom (USEPA, 1996b). According to Vedal (1997), measurement error in individual exposure results in misclassification of exposure. Misclassification, if random, may reduce the ability to detect actual risk. Misclassification, if systematic, could lead to risk associations that do not exist.

Ambient PM Concentration as a Surrogate for PM Exposure and Dosage - The health effects of PM experienced by an individual are presumed to depend upon the mass, size and composition of those particles deposited within various regions of the respiratory tract over a specific time period. In practice, when relating human health to PM pollution variables, it is necessary to use time-weighted-average (TWA) ambient PM concentration (usually over 24 hours) as a surrogate for PM exposure and PM dosage because only fragmentary data are typically available on personal exposures to PM, as discussed below. However, the USEPA's (1996b) PM Criteria document states that: "... *a total TWA personal exposure to PM (ambient PM plus indoor PM) will be a poor surrogate for the*

personal exposure to PM of ambient origin for those people whose personal exposures are dominated by indoor (residential and occupational) sources, such as environmental tobacco smoke ..." and the USEPA (1982) PM Criteria document cited several studies which found almost no correlation between personal exposure and outdoor ambient respirable PM.

Lipfert and Wyzga (1995b) raise several exposure uncertainty issues that lead to uncertainties in correlations between exposure and health outcomes. According to them, most people spend the majority of their time indoors, so that routine outdoor air sampling (often conducted at considerable distance from the individual studied), the exposure measure used in air pollution epidemiology, is subject to considerable uncertainty and potential bias as a surrogate for personal exposures. Uncertainties can occur on many levels including:

1. Partitioning observed health responses among the many confounding species of air pollutants present,

2. Combining the effects of the microenvironment (personal exposure) of the individual, including the combination of outdoor air, workplace exposures, residential and commercial indoor air exposures and air exposure inside of public and private transportation,

3. Selecting the correct surrogate exposure metric from the many options available in community monitoring networks, including cumulative exposures in mortality studies,

4. Poorly defining urban and regional variations in outdoor quality from sparse networks. Spatial variations depend strongly on averaging times, proximity to pollution sources, and atmospheric residence times,

5. Incorporating instrumental and analytical errors, which can be both random and systematic, and

6. Overlooking temporal differences, as the difference between measured outdoor concentrations and actual exposures which vary from day to day as well as by species and particle size.

Effect of Error - It has been suggested by numerical experiments that error in the exposure metric will bias the regression coefficient, depending on the nature of the error (Lipfert and Wyzga, 1995b). Lipfert and Wyzga (1995b) and Lipfert (1994) used data simulation and numerical experiments with mortality and air quality data to show that differences in the reliability of exposure estimates bias the implied relationships between correlated variables in multiple regressions. The variable whose exposure metric has the least error tends to dominate, even when the underlying relation is identical. In PM measurements, the larger error is associated with the coarse fraction (USEPA, 1996b; 1996i).

In the present context, differential measurement errors have been observed in dichotomous samples that involve separation of fine from coarse fractions of PM. Lipfert and Wyzga (1997) have demonstrated that exposure biases preclude the ability to reliably determine statistical relationships between health outcomes and exposure based on particle size.

Personal Exposure Monitoring (PEM) - Very little inter-comparison of actual (i.e., personal) exposure with air quality exposure metrics from central outdoor monitoring stations has been conducted. Those limited studies that do exist show great heterogeneity; the correlation of single central ambient PM with PEM is characterized as poorly correlated in the USEPA (1982) PM Criteria document (Pellizzari *et al*., 1993; Özkaynak *et al*., 1990; Spengler *et al*., 1985; Dockery and Spengler, 1981). In the absence of concrete data to the contrary, it is unlikely that a central ambient air monitor could adequately characterize personal exposure to deleterious components in air.

PM Monitoring Results: Long Term Averages - In most of the critical epidemiological studies underlying the new PM standard, direct measurement of $PM_{2.5}$ was not possible, hence another surrogate was used. The highest $PM_{2.5}$ concentrations are reported over eastern urban industrial centers, where the concentrations of 20 $\mu g/m^3$ to 30 $\mu g/m^3$ exceed the non urban $PM_{2.5}$ by a factor of two to three. The USEPA (1996b; 1996f) has documented the 10-year trends, seasonal patterns, relationship between $PM_{2.5}$ and PM_{10} and the fine particle chemical composition by region. Over the eastern U.S., there exists a regionally homogeneous background of $PM_{2.5}$ with smooth spatial gradients except for local hot spots confined to within a few miles of the urban industrial centers. This homogeneity is cited as evidence that eastern U.S. $PM_{2.5}$ is a secondary aerosol produced several days after the emission of gaseous precursors. It is thought that the hot spots consist of primary emissions (USEPA, 1996b). From the USEPA Aerometric Information Retrieval System (AIRS) data, $PM_{2.5}$ shows good correlation with PM_{10} for monthly averaged data in the conterminous U.S. (Correlation Coefficient = 0.82, slope = 0.56; USEPA, 1996b). Such correlations are replicated almost exactly in the western and eastern U.S. data subsets. Nationally, $PM_{2.5}$ mass accounts for about 57 percent of PM_{10} mass, with comparable fractions in the western and eastern data subsets. Brook, Dann and Burnett (1997) found similar results at Canadian sites.

Monitoring data for PM_{10} are available from a number of AIRS sites across the country. However, data for characterizing $PM_{2.5}$ and $PM_{(10-2.5)}$ as well as PM_{10} are not readily available. Data for $PM_{2.5}$ and $PM_{(10-2.5)}$ have been obtained at sites in the Interagency Monitoring of Protected Environments/Northeast States for Coordinated Air Use Management Networks, which are in remote sites. Measurements suitable for determining trends and patterns of $PM_{2.5}$ and $PM_{(10-2.5)}$ in populated areas are available from only a few sites. Most such data have been obtained with dichotomous samplers which measure $PM_{2.5}$ (an indicator of fine particles) and $PM_{(10-2.5)}$ (an indicator of the coarse fraction of PM_{10}). These two fractions may be added together to give PM_{10}. $PM_{2.5}$ is sometimes referred to as fine and $PM_{(10-2.5)}$ as coarse, although it is understood that $PM_{2.5}$ will contain that fraction of the coarse mode PM below 2.5 μm diameter and neither PM_{10} nor $PM_{(10-2.5)}$ will contain that portion of the coarse mode above 10 μm diameter.

PM Monitoring Results: Short Term Averages - According to the USEPA (1996b) PM Criteria document, data suitable for characterizing the daily variability in $PM_{2.5}$ and PM_{10} are available from only one site in southwestern Philadelphia. The National Weather Service provides daily observation of visibility, from which another correlation with fine particle concentrations can be made. Abbey *et al.* (1995b), for example, interpolated monthly statistics from the California Air Resources Board (CARB) statewide network of air monitoring stations, using mean concentration and exceedance frequency. Total suspended particles and PM_{10} data were obtained and interpolated to the ZIP code centroids of both work and home locations of study participants. Fine particles were estimated by correlation with airport visibility. The Harvard Six Cities study (Dockery, *et al.*, 1993) directly obtained data for $PM_{2.5}$ and PM_{15} every other day for several years. CARB operates about twenty sites that collect $PM_{2.5}$ and $PM_{(10-2.5)}$ data with a sampling frequency of every sixth day. Because of the small number of data sets for $PM_{2.5}$ and either $PM_{(10-2.5)}$ or PM_{10} levels, the USEPA concludes in its PM Criteria document (USEPA, 1996b) that detailed intercomparisons of the behavior of these aerosol size fractions in different regions of the U.S. cannot yet be made.

Collocated 24-hour $PM_{2.5}$ and PM_{10} filter samples were collected at a single site in southwestern Philadelphia from May 1992 through April 1995 (Koutrakis, 1995). This unique data set was collected on a nearly daily basis, thereby allowing one of the few assessments of day-to-day variability in aerosol properties. The highest median and extreme (72.6 $\mu g/m^3$) $PM_{2.5}$ concentrations were found during summer, with a difference of 50 $\mu g/m^3$ between them. PM_{10} concentrations exhibited strong maxima during both the summer (82.4 $\mu g/m^3$) and winter (77.5 $\mu g/m^3$). The difference between median and maximum values was 54.4 $\mu g/m^3$ during summer and 58.3 $\mu g/m^3$ during winter. The median PM_{10} concentration was 28.0 $\mu g/m^3$ in summer, and ranged between 19.2 $\mu g/m^3$ and 20.9 $\mu g/m^3$ during the other seasons. $PM_{2.5}$ and PM_{10} concentrations were highly correlated ($r = 0.92$). PM_{10} and $PM_{(10-2.5)}$ concentrations were less highly correlated ($r = 0.63$) and $PM_{2.5}$ and $PM_{(10-2.5)}$ concentrations were even less well correlated ($r = 0.30$). The maximum difference in day to day $PM_{2.5}$ concentrations was 54.7 $\mu g/m^3$.

The chemical composition of PM differs by region of the U.S. and by particle size. In the eastern U.S., fine particles consist mainly of sulfate and elemental and organic carbon, with some minerals and nitrate, because the aerosols are acid. Coarse particles are mainly minerals. Both of these fractions are similar in composition in the central U.S., but the fine particle composition is distinctly different in the western U.S., as elemental and organic carbon become dominant over sulfate, and minerals and nitrate assume a larger fraction (USEPA, 1996b: Appendix 6A).

Future Air Monitoring Network Plans - Since the completion of PM epidemiological data collection, the USEPA (1996b: Appendix L) has identified a *Reference Method for the Determination of Fine Particulate Matter as $PM_{2.5}$ in the Atmosphere*. This reference method identifies a single filter sampler that is both design and performance specified by the USEPA. The method provides for the measurement of ambient mass

concentrations of fine PM which have an aerodynamic diameter less than or equal to a nominal 2.5 μm ($PM_{2.5}$) in ambient air over a 24-hour period to determine whether the primary and secondary NAAQS for fine PM are met. USEPA staff recommended characteristics of a fine particle reference method include the following:

1. Promulgate a new fine particle ($PM_{2.5}$) method in addition to the current PM_{10} standard,
2. Single mass measurement for 24 hours,
3. Every day sampling without daily maintenance,
4. Capability of providing sample(s) for later chemical analysis,
5. Provide a clear quality assurance and detailed standard operating procedure for routine monitoring,
6. Readily available, inexpensive and easy to use,
7. Operate well under a wide range of ambient conditions, and
8. A sharp cut-point of the inlet and impactor at 2.5 microns Aerodynamic Equivalent Diameter (AED) to minimize coarse particle intrusion.

$PM_{2.5}$ samplers that meet all the specifications set forth in the reference method but have minor deviation and/or modifications to obtain sequential (multi-filter) operation will be designated as "Class I" equivalent methods for $PM_{2.5}$. In addition, a Class II and III equivalent method performance criteria for non-USEPA design specification samplers and automated continuous samplers have been proposed.

The reference method sampler's primary function is to manually collect PM as $PM_{2.5}$ over a 24-hour sample event. A single 47 millimeters (mm) membrane filter will be equilibrated at specified laboratory conditions and weighted on a microbalance for pre- and post-weight. Supplemental requirements for chemical analysis are being developed for areas of the country with chemical or elemental site specific conditions.

The reference method sampler consists of a PM_{10} low-flow inlet (dichotomous Inlet) that has been characterized and used for over ten years. This omni-directional inlet acts as an aerodynamic device that does not discriminate ambient PM_{10} under varying wind and climate conditions and provides a clean aerodynamic cut-point of particles greater than ten microns entering the system. Following the PM_{10} inlet is a 12-inch length of sample tube that supports the PM_{10} inlet above the sample shelter and transitions into the $PM_{2.5}$ particle size separator (impactor). The USEPA and the Research Triangle Institute in North Carolina have designed and tested a single jet impactor with an oil impregnated substrate known as the Well Impactor Ninety Six (WINS) (USEPA, 1996b; 1996i). This impactor operates as a volumetric sample rate of 16.67 liters/minute and has a sharp aerodynamic cut-point at 2.5 μm. The exit of the single jet impacts the PM_{10} fraction of ambient particles onto a 37 mm glass fiber substrate that is

impregnated with one ml of diffusion pump oil. The particles $PM_{2.5}$ AED and smaller exit the impactor well and are collected on the 47 mm filter media. A vacuum pump volumetric flow rate control system, flow rate measurement device, ambient and filter temperature monitoring system, timer, outdoor enclosure, and suitable mechanical, electrical or microprocessor monitoring control capability, meet design and functional performance requirements as specified by the USEPA (1996b: Appendix L).

The PM_{10} inlet, sample tube, WINS Impactor, filter holder, and filter cassette are design specified and mechanical drawings have only now been made publicly available by the USEPA. The remainder of the reference method sampler is performance specified and requires that the sampler provide automatic control of sample flow rate to five percent of 16.67 liters/minute, and monitor the operational parameters as well as log the ambient temperature, filter temperature, ambient barometric pressure, and system pressure every five minutes during the 24-hour sample event. This information must be available to the sampler operator during and at the end of each sample event in both visual and electronic data form. A microprocessor provides a digital display that updates continuously while RS232 data output port provides the capability of log data to be electronically output from the sampler.

Currently, there are an estimated 1,600 PM_{10} ambient monitoring sites in the U.S. Of these, the majority operates on an every sixth day sampling cycle. The proposed $PM_{2.5}$ standard will require daily sampling, but will maintain the PM_{10} requirement at every sixth day. The $PM_{2.5}$ fine particle network is proposed to be implemented over three years beginning in 1998 and may result in 600 additional future sampling sites. Requirements for "core" monitoring sites in each state are based on population, regional transport and background data. "Sub-core" sites will provide a network for trends, and "Special Purpose Sites" are for initial problem identification and research.

In August 1996, the first contract from the USEPA to build prototype Federal Reference Method Samplers (FRMS) for the determination of 2.5 μm fine particulates in the atmosphere was awarded. A second USEPA contract has been awarded FRMS for the National Particle Research Network. Hence, the data to perform adequate ambient $PM_{2.5}$ analyses will only become available in the future.

Plausibility of a Causal $PM_{2.5}$/Mortality Relationship - The evidence presented to CASAC for a causal PM/mortality relationship is strong for a number of historical air pollution episodes like Donora, Pennsylvania in the 1940s and London, England in the 1950s. During these episodes, PM concentrations were estimated to be as high as 1000 $\mu g/m^3$ to 2000 $\mu g/m^3$ (USDHEW, 1969). However, the central question is whether PM is causing premature mortality today at PM concentrations that are generally two orders of magnitude lower than in the historical episodes. Nationwide, annual average PM_{10} concentrations are less than 25 $\mu g/m^3$ while the maximum 24-hour concentration observed in a given year is considerably less than 100 $\mu g/m^3$ (USEPA, 1996f). In Michigan, the statewide annual average PM_{10} concentration is about 20 $\mu g/m^3$ and the 24-hour maximum concentration average is 70 $\mu g/m^3$ across the state (MDEQ, 1996).

The Case for a Causal Relationship - The case for a causal relationship between presently observed $PM_{2.5}$ concentrations and mortality is based primarily on epidemiological studies. There are two types of PM epidemiological studies, acute and chronic. In the acute studies, statistical associations between some measure of daily PM concentrations and daily mortality have been observed. There have been many studies of this type reported in the literature (see Appendix 2). There are two types of chronic epidemiological studies, cross-sectional studies and prospective cohort studies. In the cross-sectional studies, a measure of the annual average PM concentrations is related to annual average mortality across various geographic units. In the prospective cohort studies, the mortality rate of individuals, whose health and demographic data are collected, is related to an annual average measure of PM concentrations. The results of three cross-sectional and three prospective cohort studies were considered in the USEPA (1996b) PM Criteria document.

Proponents of USEPA's new fine particle standard base their case on the consistency and coherence of the epidemiological studies. They base the selection of 2.5 μm as the upper diameter for the fine particles primarily on the results of the Six Cities study. Below are the proponent's arguments.

Consistency of Results. A number of acute epidemiological studies have consistently found a statistically significant association between the daily variation in some measure of PM and mortality in cities in the U.S., Canada, Latin America, United Kingdom and continental Europe. The strength of the association was similar across a wide range of geographic regimes, climatic conditions, and mixtures of various air pollutants. The association was found regardless of the measure of PM used. The measures used included, TSP, PM_{10}, $PM_{2.5}$ (one study), sulfates, coefficient of haze, British smoke and visibility. Since sulfates, coefficient of haze, British smoke and visibility correlate best with $PM_{2.5}$, this provides circumstantial evidence that $PM_{2.5}$ is the component of concern (USEPA, 1996b; 1996f; 1996i). In addition, all of the chronic studies with one exception, found consistent positive relationships with annual mortality and a measure of annual PM. The one that did not find a consistent relationship suffered from poor statistical power and a questionable measure of PM exposure.

Supporters of a causal PM/mortality relationship argue that such consistent results cannot be due to chance and thus are at least strongly suggestive of causality. Further, such consistent results cannot be due to confounding by weather or other air pollutants. Moreover, such consistent results strongly suggest that concerns over exposure misclassification are unfounded.

Coherence of Results. The results from the acute and chronic mortality studies and the chronic morbidity studies fit together to present a coherent picture that strongly supports the cause and effect hypothesis. The excess mortality predicted by the chronic studies is roughly three times that of the acute. On days when excess mortality from cardiovascular and respiratory disease is observed, higher PM concentrations, excess hospitalizations for cardiovascular and respiratory disease are reported. These mortality and morbidity excesses are greatest in the elderly, the population that would be expected to be most susceptible. On days of high PM, the proportion of deaths from

lung and heart disease is higher than on low PM days. These findings are all supportive of a causal role for PM.

The Case for $PM_{2.5}$. Since there is usually a high degree of interrelation between different air pollutant species because of common sources and meteorological influences, the preceding discussions make a compelling case for a causal relationship between mortality and air pollution. Whether or not the actual causal agent is PM or some other component of air pollution, PM is the best measure of the causal agent because it consistently has had the strongest relationship with mortality. In two direct comparisons, $PM_{2.5}$ consistently showed a stronger statistical relationship with mortality than either PM_{15} (PM_{15} is approximately equal to PM_{10}) or $PM_{15-2.5}$ (the fraction of the PM_{15} with a diameter between 2.5 μm and 15 μm). In the acute Six City analysis (Dockery *et al.*, 1996), five out of the six cities showed that $PM_{2.5}$ had the strongest association with mortality. In the prospective cohort Six City study, the correlation between $PM_{2.5}$ and excess mortality was almost perfect. In addition, many of the epidemiological studies used some constituent (sulfate) of $PM_{2.5}$ or some measure of $PM_{2.5}$ (visibility, coefficient of haze, or British smoke) and found consistent positive results (see Appendix 2). In addition, because of the nature of the fine particles (combustion products and secondary particles) and their chemical composition (acids, polynuclear aromatics, heavy metals etc.), they are more biologically active than the coarse particles which are composed mainly of crustal and soil dust.

The Case Against a Causal Relationship - Those opposed to the USEPA's fine particle standards argue that the results are not consistent, cast doubts that coherence has been demonstrated, stress the absence of a plausible biological mechanism, and question the appropriateness of the exposure data. Their arguments are summarized below.

Inconsistency of Results. When the results of a number of reanalysis studies are considered, the consistency argument is brought into question. These studies have been reported by Samet *et al.* (1997), Davis *et al.* (1996), Moolgavkar and Luebeck (1996), Li and Roth (1995a; 1995b), Lipfert (1995), Lipfert and Wyzga (1995a; 1995b), Moolgavkar *et al.* (1995a; 1995b), Samet *et al.* (1995) and Styer *et al.* (1995),

Lipfert and Wyzga (1997) show that the larger error associated with the Six City measurement of the coarse particles ($PM_{10-2.5}$) precludes the conclusions that the fine particles are the more important fraction in terms of explaining mortality. Further, they conclude that it is necessary to include gaseous pollutant as well as PM to provide robust estimates of the responsibilities for the implied mortality gradients. Based on their reanalysis of previous studies, this latter conclusion is essentially the same conclusion reached by Moolgavkar *et al.* (1995a; 1995b), Moolgavkar and Luebeck (1996), Lipfert and Wyzga (1995a; 1995b), Lipfert (1995), Samet *et al.* (1995), and Samet *et al.* (1997). In each study, these investigators reanalyzed an original data set but included additional gaseous pollutants, and in each case, the result indicated that no single pollutant could be identified as the causative agent. Moolgavkar et. al. (1995a), Lipfert and Wyzga (1995a), Samet *et al.* (1995) and Samet *et al.* (1997)

reanalyzed the Philadelphia data originally examined by Schwartz and Dockery (1992a) and could not identify PM as being more associated with mortality than other gaseous pollutants. Moolgavkar *et al.* (1995b) reanalyzed the Stubenville, Ohio data set originally reported by Schwartz and Dockery (1992b) and found that the addition of sulfur dioxide to the analysis substantially attenuated the PM/mortality relationship and it was no longer statistically significant. Moolgavkar and Luebeck (1996), Lipfert and Wyzga (1995b), and Lipfert (1995), come to the same conclusions concerning the cross-sectional and prospective cohort studies as well. These results are not supportive of PM or $PM_{2.5}$ as the only cause of the increased mortality.

Styer *et al.* (1995) examined data from Salt Lake County in Utah, which is adjacent to the Utah Valley County where Pope *et al.* (1992) reported a positive PM/mortality relationship. However, Styer *et al.* (1995) found no relationship between mortality and any pollutant including PM. In the same report, Styer *et al.* (1995) also examined Cook County data segregated by season and found a positive PM/mortality relationship in the fall and spring but not during the summer and winter. Samet *et al.* (1997) also segregated the Philadelphia data set by season and found that the pollutant that best described excess mortality in the winter was ozone, which is not plausible because of the extremely low concentrations that exist in winter.

Li and Roth (1995a) using Philadelphia data, Li and Roth (1995b) using Philadelphia, Birmingham and Toronto data, and Davis *et al.* (1996) using Birmingham data concluded that the answer obtained from the analysis is highly dependent on the method of treating temperature, the model employed and the lag variables considered. They show that positive and negative associations, as well as no relationship solutions, can be found depending on the choice of these parameters. They also conclude that there are no absolute standards for choosing any one model as the correct model.

In summary, the reanalysis studies attenuate support for the consistency argument. They cast doubt on the selection of $PM_{2.5}$ as the causal agent as well as raise questions regarding the appropriateness of the statistical methods used in particular epidemiological studies. Additional discussions of these points can be found in Gamble and Lewis (1996).

The Coherence Issue. All of the studies that are used to demonstrate the coherence of the mortality and morbidity endpoints are epidemiological studies. Thus, they all are subjected to the uncertainties discussed in the previous section. This is discussed in greater detail in Gamble and Lewis (1996).

Cross-sectional and Prospective Cohort Studies. None of the three prospective cohort studies have been subjected to reanalysis to determine whether the conclusions reported by the original investigators are robust. The reason for this is that unlike the acute and cross-sectional studies, the mortality data in the cohort studies are not publicly available. However, the comments made about the cross-sectional studies will also apply to the prospective cohort studies because of their similar design.

Lipfert (1995) and Lipfert and Wyzga (1995a) reanalyzed Lipfert (1993) and showed that the relationship between PM and mortality greatly diminished when additional confounders, particularly personal lifestyle risk factors, are included. In addition, depending on the model employed, different pollutants were identified as being significantly associated with mortality. In addition, it was pointed out that the regression coefficients (in deaths/unit of PM) will be biased on the high side because of significant improvements in air quality during the last decade of exposure. For example, Pope *et al*. (1995) used 1979 - 1983 estimates of PM exposure and did not take into account that ambient concentrations of PM (as well as SO_2) in urban areas over the previous 10 years to 15 years decreased drastically largely because of sulfur limitations in stationary-source fuels. For example, in New York City, the average concentration of TSP in 1972 was about 110 $\mu g/m^3$ (the peak site was about 140 $\mu g/m^3$). By 1977, the average deceased to about 64 $\mu g/m^3$ (Ferrand, 1978). By 1987, TSP averaged about 50 $\mu g/m^3$. In 1970, SO_2 averaged about 0.084 ppm in New York, but by 1977 it was only 0.028 ppm. In 1992, the mean was 0.019 ppm. In 1965, sulfates averaged 35 $\mu g/m^3$ in New York (Eisenbud 1978). By 1975, it was about 12 $\mu g/m^3$ and now it is about six $\mu g/m^3$. Thus, TSP declined by a nearly a factor of two over a five-year period, sulfur dioxide by nearly a factor of three over a seven-year period, and sulfates by a factor of three over a 10-year period. Such decreases by themselves can more than explain the discrepancies in the regression coefficients between the cross-sectional studies and the time-series studies. These decreases were not limited to just New York. Two sites in Detroit averaged 94 $\mu g/m^3$ and 130 $\mu g/m^3$ of TSP in 1974 and both decreased to 60 $\mu g/m^3$ by 1981. At both of these sites, the coefficient of haze, a measure of fine particles, experienced about a two-fold decrease (Wolff, Stroup and Stroup, 1983).

In summary, these studies do not unambiguously identify PM as the pollutant most strongly associated with premature chronic mortality. In addition, the strength of any association is dependent on the model chosen and the inclusion of potential confounders. Finally, any estimates derived from some studies are likely to be biased high due to the use of recent air quality data as a measure of long-term exposure.

Biological Plausibility. Several of the CASAC members, including one of the respiratory physicians stated that there is no biologically plausible mechanism that could explain the apparent relationship between acute mortality and PM at concentrations that are a fraction of the present PM_{10} NAAQS (Wolff, 1996c). This has lead some to postulate that the acute mortality is actually a “harvesting” effect (i.e., individuals who are terminally ill die somewhat prematurely due to the additional stress caused by PM or overall air pollution). While this may explain some or most of the acute deaths, it cannot explain the apparent long-term, chronic deaths attributed to annual PM concentrations in the prospective cohort studies. These prospective cohort studies discussed above, suggest that the acute mortality only accounts for about a third to a half of the total deaths attributed to PM. However, all or most of this discrepancy disappears when additional potentially confounding variables are included in the cohort studies and historical or cumulative rather than concurrent air pollution exposures are considered (Lipfert, 1995).

Exposure Misclassification. The exposure misclassification concern revolves around the validity of the assumption made in all of the acute studies that daily ambient PM data collected from a centrally located air monitoring site is representative of personal exposure to PM. More studies cited in the USEPA (1996b) PM Criteria document show poor or no relationship between personal exposure and a central monitor than those that do. This is to be expected since people spend about 85 percent of their time indoors (USEPA, 1996c; 1989). Furthermore, about one-third of the reported daily mortality occurs in hospitals. There are no data that show any relationship between ambient air and filtered hospital air.

The shape of the dose-response function is also a concern. Because of measurement errors, the present statistical methodologies are incapable of detecting the existence of a possible threshold concentration below which acute mortality would not occur.

Particulate Matter Conclusions - The Panel concludes that there are significant, adverse human health effects associated with increases in environmental air pollution variables. Epidemiological studies have repeatedly shown statistically significant associations of air particulate matter levels with a variety of human health endpoints including increased hospitalizations and deaths from cardiorespiratory disease. Controversy currently remains regarding the nature and impact of confounding factors, the biological mechanism(s) which might be involved, the validity of exposure measures and, consequently, whether $PM_{2.5}$ causes the reported health effects. Additional epidemiological, toxicological and exposure matrices research are needed to resolve these controversies.

Ozone

Human Health Assumptions - The USEPA presented its human health assumptions, interpretations and conclusions for its ozone air quality rules in its Ozone Criteria document (USEPA, 1996a) and its August 1995 draft and June 1996 Staff papers (USEPA, 1995; 1996h). The following is a summary of the health basis for the ozone standard and CASAC's interpretations and consensus recommendations (Wolff, 1996b; 1995). Unlike with PM, CASAC did reach consensus on the range of the standard.

Health Effects Studies - The USEPA (1996h; 1995) ozone review relied on four broad types of health effect studies: animal studies, controlled human chamber studies, field studies of ambient exposures, and hospital admission studies. The main use of the animal studies was to gain insight on the mechanisms by which ozone produces biological responses and damage to the respiratory system. In the controlled human exposure studies, individuals were typically exposed to ozone concentrations slightly above, at or below the NAAQS for a number of hours (approximately six hours is the most common) while engaged in light to heavy exercise. Before, during and after the exposure, the individual lung functions (such as forced expiratory volume - FEV_1, which is the maximum volume of air that can be expired in one second) are monitored and any symptoms (cough, shortness of breath, chest pain, etc.) are noted. These studies

produced two important results. First, for one or two hour exposures, decrements in lung function tests and symptoms were noted only at concentrations greater than three times the one-hour NAAQS in individuals not engaged in exercise. However, some exercising individuals when exposed for longer periods experience decreased lung-function test performance and symptoms even at concentrations at or below the one-hour NAAQS. This is part of the evidence that suggested a multiple hour (8-hours) NAAQS would be more appropriate than a one-hour standard.

Field studies consisted of summer camp and adult exercise studies. In the summer camp studies, children, engaged in the normal physical activities that occur at summer camps, participated in lung function testing and the results were correlated with ambient ozone concentrations. In the adult exercise studies, lung function tests were administered to joggers before and after they ran outdoors and the test results were also correlated with ambient ozone concentrations. The results of both types of studies showed a small but statistically significant relationship between decreased performance on the lung function tests with increasing ozone at concentrations at and below the one-hour NAAQS. These results are consistent with the controlled chamber studies. Furthermore, since the relationship between the lung function test results and ozone appears to be linear at low exposure levels, there may not be a threshold concentration below which biological responses will not occur.

The hospital admission studies examined the relationships between daily ozone concentrations and daily hospital admissions for respiratory causes. These studies have consistently shown an apparent linear relationship in various North American locations between ozone and the admissions, and the USEPA has assumed that this relationship is cause and effect. The relationship has been shown to remain even when considering only concentrations below the one-hour NAAQS. Thus, there is no evidence of a threshold concentration and this reinforces the conclusion from the field studies.

CASAC'S Interpretations - Based on a review of the material compiled by the USEPA (1996h; 1995), it was the consensus of the CASAC members that an eight-hour standard was more appropriate for a human health-based standard than a one-hour standard, but it was pointed out that a one-hour or an eight-hour standard could be designed to provide the same degree of protection by setting the level of either measure appropriately. CASAC unanimously agreed that the one-hour standard be eliminated and replaced with an eight-hour standard. It was also the consensus of the members that the form of the eight-hour standard should be more robust than the one-hour standard. The one-hour standard was based on an extreme value statistic which is significantly dependent on stochastic processes such as extreme meteorological conditions (Wolff, 1996b; 1995).

Based on its review of the literature, CASAC felt that the weight of the health effects evidence indicated that there was no threshold concentration for the onset of biological responses due to exposure to ozone above background concentrations. Based on information now available, it appears that ozone may elicit a continuum of biological

responses down to background concentrations. It should be noted that a biological response does not necessarily imply an adverse health effect. Nevertheless, this means that the paradigm of selecting a standard at the lowest-observable-effects-level and then providing an "adequate margin of safety" is not possible. It further means that risk assessments must play a central role in identifying an appropriate level (Wolff, 1996b).

USEPA Risk Assessment - In order to conduct the risk assessments, the USEPA needed to identify the populations at risk and the physiological responses of concern, develop a model to estimate the exposure of this population to ozone, and develop a model to estimate the probability of an adverse physiological response to the exposure. The USEPA selected a small segment of the population, "outdoor children" and "outdoor workers," particularly those with preexisting respiratory disease as the appropriate populations with the highest risks (USEPA, 1996h). CASAC concurred with the USEPA that the models selected to estimate exposure and risk were appropriate models. However, because of the myriad of assumptions that are made to estimate population exposure and risk, large uncertainties exist in the model estimates (Wolff, 1996b).

The results of two of the risk analyses are presented in the USEPA (1996h) Staff paper and are reproduced in Tables 3 and 4. The numbers in these tables differ slightly from the numbers presented in the CASAC November 30, 1995 closure letter (Wolff, 1995), which were based on USEPA's estimates that were in an earlier (August) draft of its Staff paper (USEPA, 1995). The numbers in Tables 3 and 4 are based on newer USEPA (1996h) estimates. The ranges from ten model runs of the risk estimates across nine cities for outdoor children are presented in Table 3. Because of the large number of stochastic variables used in the exposure model, the exposure estimates vary from run to run. However, the ranges presented in Tables 3 and 4 are not reflective of all of the uncertainties associated with the numerous assumptions that were made to develop the estimates (Wolff, 1996b).

Based on the results presented in these and other similar tables contained in the USEPA (1996h) Staff paper and an acknowledgment that all the uncertainties cannot be quantified, CASAC concluded that there is no "bright line" which distinguishes any of the then proposed standards (either the level or the number of allowable exceedences) as being significantly more protective of public health. For example, the differences in the percent of outdoor children (Table 3) responding between the present standard (1H1EX at 0.12 ppm) and the most stringent proposal (8H1EX at 0.07 ppm) are small and their ranges overlap for all health endpoints. In Table 4, the estimates in row one suggest considerable differences between the several options. However, when ozone-aggravated asthma admissions are compared to total asthma admissions (Rows 5 and 6), the differences between the various options are small. Table 4 also contains the 90 percent confidence interval for a few of the estimates (Columns 1, 5, 8, and 9) which indicate that none of the differences are statistically significant (Wolff, 1996b).

The results in Table 4 address questions concerning the reasonableness of the assumption of a linear relationship between admissions and ozone concentrations. For example, if New York City was just meeting the present NAAQS of 0.12 ppm (1H1EX 0.12), Table 4 indicates that ozone would be responsible for 890 admissions per year. However, of that 890, only 210 admissions would be due to ozone concentrations above the summer background concentration which is taken here to be 0.04 ppm. The majority (680 or 76.4%) of the admissions are attributable to ozone exposure when the ozone concentrations were less than or equal to the summertime background (Wolff, 1996b).

Table 3. Range of median percent of outdoor children responding across nine U.S. urban areas upon attaining alternative air quality standards.[a]

Health Endpoints	Range of Median Risk Estimates Associated With Just Attaining Alternative Standards (percent of outdoor children responding)							
	Alternative One-Hour NAAQS		Alternative 8-Hour Daily Maximum Standards					
			One Expected Exceedance Standards				Five Expected Exceedance Standard	
	1H1EX[1] 0.12 ppm	1H1EX 0.10 ppm	8H1EX 0.10 ppm	8H1EX 0.09 ppm	8H1EX 0.08 ppm	8H1EX 0.07 ppm	8H5EX 0.09 ppm	8H5EX 0.08 ppm
FEV_1 decrement ≥ 15%	5-14	3-9	7-16	5-12	3-8	2-5	5-14	3-10
FEV_1 decrement ≥ 20%	1-6	0-4	2-7	2-5	1-3	0-1	2-6	1-4
Moderate or Severe Pain on Deep Inspiration	0	0	0-1	0	0	0	-	-
Moderate or Severe Cough	0-1	0	0-1	0-1	0	0	-	-

(a) Estimates for alternative NAAQS with 1 exceedance from USEPA, 1996h: Table V-18, estimates for NAAQS with 5 exceedances from USEPA, 1995:Table VI-1.

(1) 1H means 1-hour standard; 1EX means 1 allowable exceedance per year.

Table 4. Estimated annual hospital admissions for asthmatics in the New York City area.

	1H1EX 0.12	1H1EX 0.10	8H1EX 0.10	8H1EX 0.09	8H1EX 0.08	8H1EX 0.07	8H5EX 0.09	8H5EX 0.08	AS IS
Excess Admissions[1]	207 70-344	130	240	180	115 39-191	60	180	120 41-199	388 132-644
% D from present std	0%	-37%	+16%	-13%	-44%	-71%	-13%	-42%	+87%
Excess + background[2]	909 308-1509	810	920	860	804 273-1336	740	860	797 270-1320	1065 361-1770
% D from present standard	0%	-11%	+1%	-5%	-12%	-19%	-5%	-12%	+17%
All Asthma Admissions	29,810	29,733	29,843	29,783	29,718	29,663	29,783	29,723	29,990
% D from present standard	0%	-0.3%	+0.1%	-0.1%	-0.3%	-0.5%	-0.1%	-0.3%	+0.6%

(1) Excess asthma admissions attributed to ozone levels exceeding a background concentration of 0.04 ppm; the values with ranges (90% confidence intervals) are from USEPA, 1996h: Table V-20; single value estimates are from USEPA, 1996h: Figure V-17.

(2) Asthma admissions included in (1) plus those due to background ozone concentrations; admissions due to background = 1065 - 388 = 677.

Ozone Conclusions - A new eight-hour ozone NAAQS of 0.08 ppm concentration was approved on June 25, 1997. Compliance will be determined by averaging the fourth highest eight-hour value each year for three consecutive years. The Panel acknowledges that the lower the standard the lower the exposure which should result in a lower biological response assuming, as current data suggest, there is no threshold concentration for ozone. The new standard was selected at the midpoint of the USEPA's proposed range of 0.07 ppm - 0.09 ppm with one to five allowable exceedences. Health risk estimates associated ozone concentrations within the proposed range as calculated by the USEPA indicated small differences which, because of uncertainties in exposure and dose-response relationships, could be considered as within the margin of error of the estimates. Therefore, selection of the new eight-hour standard of 0.08 ppm from among the proposed ranges of values appears to be a policy decision.

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DIRECTIVES 2 & 3. Identify and evaluate the validity of the key air quality and human health assumptions contained in the NRDC report. Identify and evaluate the appropriateness of the methodology used to develop NRDC estimates of mortality and determine if there is sufficient evidence to attribute causality.

Introduction

In May 1996, the NRDC published a report entitled, *Breath-Taking Premature Mortality Due to Particulate Air Pollution in 239 American Cities* (Shprentz, Bryner and Shprentz, 1996). While briefly acknowledging other epidemiological studies, the report relies on two long-term studies, Six Cities study (Dockery *et al*., 1993) and American Cancer Society (ACS) study (Pope *et al*., 1995), to develop an estimate of the extent of premature mortality attributable to PM air pollution in 239 U.S. metropolitan areas. The report concluded that approximately 64,000 people may die prematurely from heart and lung disease each year due to particulate pollution and that lives are being shortened on average by one to two years rather than by days and weeks in the most polluted areas. Among its recommendations, the report calls for the USEPA to revise the NAAQS to establish standards for fine particulates ($PM_{2.5}$) and PM_{10} at levels that will protect public health with an adequate margin of safety.

The NRDC study identifies a series of limitations and uncertainties with its analysis. According to Shprentz, Bryner and Shprentz (1996), there are uncertainties about whether, (1) PM as a whole, or as a specific constituent, is a harmful agent, (2) PM causes increased cardiopulmonary illness, or exacerbates existing conditions, contributing to premature mortality, and the mechanism involved in producing these effects, (3) there is a threshold below which health effects do not occur, (4) statistical expressions of risk, which convey a probability that an association exists, prove causality and (5) data from a central monitoring station can characterize air pollution concentrations for a large geographic area. In addition, there are uncertainties about (6) the composition of particulate matter in different areas of the country, (7) the relationship between PM_{10} and $PM_{2.5}$ concentrations, (8) the relative importance of indoor versus outdoor exposures, and (9) historic PM_{10} and $PM_{2.5}$ concentrations.

According to Shprentz, Bryner and Shprentz (1996), in order to perform a quantitative analysis, the NRDC needed to make a number of general air quality and human health assumptions about the identified uncertainties. The key air quality assumptions were: (1) a limited number of monitoring stations can be used to characterize ambient concentrations and exposures for an entire Metropolitan Statistical Area (MSA) and (2) PM_{10} monitoring data can be converted to estimate $PM_{2.5}$ concentrations using a factor of 0.60. The NRDC human health assumptions were: (1) the associations reported in the epidemiological literature between particle concentrations and premature mortality are indicative of a cause and effect relationship, (2) there is a linear relationship between particle concentration levels and risk of premature mortality, (3) there does not exist an identifiable threshold below which there is no relationship between particle levels and mortality and (4) the health effects occur at relatively low concentrations.

Table 5 outlines the basic methodology used by the NRDC to conduct its analysis. Annual arithmetic mean concentration PM_{10} data were obtained for the period 1990 - 1994 from government monitoring stations located in residential, commercial and industrial areas within 239 MSAs. For MSAs with more than one monitor, an average annual mean PM concentration was calculated for each year of data. The yearly averages were then averaged to derive a single average annual mean PM concentration for each MSA. In order to derive a value for $PM_{2.5}$, a factor of 0.60 was applied to the PM_{10} data obtained.

Table 5. Methodology used by the NRDC to develop and evaluate its base case estimate of mortality.[(a)]

1.	Collection and analysis of particulate monitoring information for major U.S. urban areas.
2.	Collection and tabulation of data on adult mortality from specified causes in major U.S. urban areas.
3.	Calculation of a risk coefficient from data presented in the ACS study.
4.	Application of the risk coefficient to city-specific monitoring data and mortality data.
5.	Performance of sensitivity analysis to evaluate the effect of alternative assumptions on the results.

(a) From Shprentz, Bryner and Shprentz (1996).

Cardiopulmonary mortality data for 1989 were obtained and adjusted to include only the adult population over 25 years of age for each MSA. Using data from the ACS (Pope *et al*., 1995) study, a regression coefficient for the relationship between fine particle levels and adult deaths from cardiopulmonary deaths was obtained. The coefficient was applied to the calculated annual mean fine particle concentrations for each urban area to obtain a city-specific adjusted rate ratio. The city-specific ratio was then multiplied with the actual city-specific mortality data to calculate the annual number of adult cardiopulmonary deaths attributed to particle pollution. The mortality figure of 64,000 is the sum of the estimated deaths per year for all 239 MSAs.

In order to evaluate the effect of alternative assumptions on its base case result, the NRDC performed a sensitivity analysis. The analysis consisted of looking at a series of cases with different assumptions (e.g., using “all cause” verses cardiopulmonary mortality; excluding industrial area monitoring data from the analysis, etc.) and then comparing these results with the result obtained for its base case. According to Shprentz, Bryner and Shprentz (1996), while a number of alternative assumptions led to lower estimates of mortality, most of the cases led to higher estimates of mortality and in all cases analyzed there was considerable overlap in the derived ranges. The authors concluded that their sensitivity analysis showed that the NRDC base case analysis represented a reasonable assessment of mortality attributed to air pollution.

Discussion

In its review of the current epidemiological literature which examined the relationship between PM and human health effects, the USEPA (1996b) cautioned "... [that while] *long-term studies provide support for the existence of short-term PM exposure effects* [on] *mortality ... and the fact that they also point toward the likelihood of chronic PM exposure effects above and beyond the simple summation of acute mortality effects, ... they are equivocal as to all the specific pollutants involved, ... they do not exclude the existence of pollutant thresholds, and quantitative estimates of cumulative PM exposure effects beyond acute impacts cannot yet be confidently stated*.**"**

According to Shprentz, Bryner and Shprentz (1996),"[The] ... *NRDC's analysis applie*[d] *the findings of the recent epidemiological studies to metropolitan areas in the U.S. ...* [I]*t ... extrapolate*[d] *the findings from epidemiological studies to other U.S. cities ...* [and] *... applie*[d] *the relationship observed in the study of the American Cancer Study cohort to current particle concentrations in U.S. cities in order to gauge the extent and significance of the particle pollution problem.*" Consequently, the air quality and human health assumptions made and the methodology used by the NRDC as a basis to permit its calculation of premature mortality were based on previously published epidemiological papers, and, in particular, the ACS (Pope *et al*., 1995) study.

A review of the various epidemiological, toxicological, meteorological and human exposure assumptions that currently drive the PM debate has been presented earlier in this report. Of the six air quality and human health assumptions used by the NRDC in its report, probably the one which has the greatest support (although not unanimous, since geography appears to have an influence - see Vedal, 1997) among the various scientific reviewers is the assumption that that $PM_{2.5}$ may be reasonably estimated by applying a factor of 0.60 to PM_{10} data. According to Shprentz, Bryner and Shprentz (1996), the factor was taken primarily from the ACS (Pope *et al.*, 1995) study for $PM_{2.5}$ although other studies with conversion factors ranging from 0.55 to 0.80 were also consulted (Iverson, 1995; Bahadori *et al.*, 1995; Burton, Suh and Koutrakis, 1996; Dockery and Pope, 1994; Spengler and Thurston, 1983). However, as indicated by this and other reviews (USEPA, 1996b and Vedal, 1997), differences of opinions across scientific disciplines continue to prevent a consensus regarding the validity of the five remaining assumptions.

Shortly after completing its report, the NRDC received several supporting statements regarding the conclusions reached (and to a lesser degree, the methodology used) in its report (NRDC, 1996b). To the Panel's knowledge, however, there has only been one review of the report (Brown, 1996). The non-peer reviewed paper identifies several areas where the author feels that the NRDC relied on unverified assumptions regarding exposure, sample representativeness, exposure-response relationship and base mortality rates from the ACS (Pope *et al*., 1995) study. The author also identified areas where he felt that the NRDC incorrectly used certain statistical applications. Based on his identification and analysis of the problems in the NRDC report, Brown (1996)

concluded that the NRDC's estimate that 64,000 people may die prematurely from cardiopulmonary disease each year due to particulate air pollution was unwarranted.

In addition to the issues identified by Brown (1996), the Panel identified a concern with the NRDC's ascribing 1990 - 1994 PM_{10} data to 1989 mortality data in order to calculate a projection of future mortality resulting from PM pollution. While the magnitude of the impact on the final mathematical projection is unknown, it does entail the need to add an additional procedural assumption. It would be necessary to assume that either all variables that could have accounted for the observed mortality in 1989 remained unchanged throughout the period 1990 - 1994 or that all variables which resulted in the measured PM_{10} values in 1990 - 1994 were the same in 1989. The NRDC report provides no data to support either assumption.

In late May 1996, the NRDC released an addendum to its report (NRDC, 1996a) which reviewed new air quality attributable mortality estimates developed by the USEPA (1996i) for portions of Philadelphia and Los Angeles. Based on its review, the NRDC indicated that the new mortality estimates developed by the USEPA were consistent with the numbers reported by the NRDC and, therefore, confirmed the methodology used by the NRDC. Both the NRDC and the USEPA relied upon statistical relationships established, in particular, in the ACS (Pope *et al*., 1995) study to develop their mortality estimates (Jones, 1997; USEPA, 1996b; 1996i; Shprentz, Bryner and Shprentz, 1996). In May 1997, Jones (1997) issued a non-peer reviewed paper critical of the USEPA's (1996i) methodology and resulting estimates indicating that the agency had incorporated mislabeled data points from the ACS (Pope *et al*., 1995) study and had calculated benefits at levels below the level of the proposed standard. According to Jones (1997), the first error results in an overestimation of annual mortality from $PM_{2.5}$ and the second error results from an overstatement of the number of cities at risk (only 10 urban areas would need to improve air quality in order to meet the PM standard). Assuming that Jones' (1997) assessment is accurate, a correction of the identified errors would reduce the USEPA's estimate of potential lives saved from 20,000 to 15,000 (Error 1 only) and 20,000 to 840 (Errors 1 and 2). Applying similar percentage decreases resulting from the errors identified by Jones (1997) to the NRDC estimate would reduce the potential lives saved from 60,000 to 45,000 (Error 1 only) and 60,000 to 2,520 (Errors 1 and 2). To date, the USEPA (1997) has acknowledged only the first error identified by Jones (1997).

Conclusions

Based on the findings reached by the Panel in Directive 1 of this report, the Panel concludes that the air quality and adverse human health assumptions and predictions used by the NRDC in its report cannot be definitively determined to be valid or invalid given the current lack of conclusive epidemiological, toxicological, meteorological and human exposure data, and the resulting differences in scientific interpretation of existing data. The particular methodology used by the NRDC to develop its estimate is not unreasonable if used under an operating assumption that PM causes increased mortality and if

correctly calculated. However, a majority of the Panel concludes that the value obtained by the NRDC for the number of premature deaths (64,000) attributed to PM in air cannot be considered reliable because of a recently recognized statistical error involved in its calculation and an uncertain causal relationship between $PM_{2.5}$ exposure and mortality.

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MINORITY STATEMENT

There is general consensus in the scientific community that current particulate and ozone air pollution levels increase heart and lung related dysfunction and death. The report downplays this consensus and over emphasizes areas of disagreement. Major areas of scientific consensus include the following:

1. Almost all human studies performed show an increase in mortality and morbidity for current levels of air pollution. These studies have been extensively reviewed without significant changes being made in the consensus on their findings. Reanalysis of some of these studies have been conducted by three different groups. Two of the three groups have confirmed the increased deaths but have cautioned that particulate air pollution alone may not be the cause, but possibly some other or additional component of air pollution (Samet *et al.,* 1997; Moolgavkar *et al*., 1955b). Seventeen of the 21 members of the USEPA's CASAC agreed that $PM_{2.5}$ was an important measure of particulate air pollution and should be regulated. What the committee could not agree upon was what the new standard should be (Wolff, 1996a). Similarly, there was consensus among the CASAC that the ozone standard needed to be lowered but again not on what the level should be (Wolff, 1995).

2. There are no animal studies of particulates which have been conducted which contradict the adverse effect found in studies on people. Animal inhalation studies at levels of particulate pollution that are currently occurring in the U.S. have not been completed. Biologic mechanisms to explain the adverse effects found in studies of humans have been proposed (Wilson and Spengler, 1996). Existing animal studies do not negate the biological plausibility of the studies on humans and there are additional animal studies not reviewed by the Panel that add more support to the biological plausibility that particulates cause the disease and death found in people (Takano *et al*., 1997; Gavett *et al*., 1996; Chen *et al*., 1995; Miller *et al*., 1995; Sioutas, Koutrakis and Burton, 1994).

3. Intervention studies showing a reduction of adverse effects in human populations with a reduction of PM level cannot be conducted until the PM levels are lowered. One such study which was performed in relation to the temporary closing of a steel mill did show a reduction in hospital admissions (Pope *et al.,* 1992). Intervention studies are usually conducted years after a public health intervention is implemented. The lack of such studies before the intervention do not cast doubt on a causal relationship between particulate pollution and disease.

4. The NRDC report used an accepted and probably conservative procedure for estimating the annual number of deaths attributed to current levels of particulate air pollution. A mathematical error acknowledged by the USEPA (1997) would lower the NRDC estimate from 60,000 to 45,000 premature deaths per year. Given the uncertainty in developing risk estimates there is clearly a range around this estimate. However, the value obtained by the NRDC is of sufficient reliability to allow a conclusion that the potential risk is not trivial (more than a few deaths) and not catastrophic (less than hundreds of thousands of deaths).

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APPENDIX 1

November 21, 1997 and December 4, 1996 Letters from Governor John Engler to the Michigan Environmental Science Board

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November 21, 1996

Dr. Lawrence Fischer, Chair
Michigan Environmental Science Board
Lewis Cass Building, 2nd Floor
P.O. Box 30026
Lansing, Michigan 48909

Dear Dr. Fischer:

The U.S. Environmental Protection Agency (EPA) is currently reviewing the National Ambient Air Quality Standards for particles and ozone. The EPA is under court order to complete its review for particles by November 29, 1996. In June 1996, the EPA Clean Air Scientific Advisory Committee (CASAC) recommended that a standard for fine particulate matter ($PM_{2.5}$ - particles with diameters $\leq$ 2.5 μm) be established, but there was no consensus on the level, averaging time or form of the standard. In May 1996, the Natural Resources Defense Council (NRDC) released a report based on a 1995 data base compiled by the American Cancer Society and analyzed by Brigham Young and Harvard Universities. This report purports that a substantial number of people die earlier than would otherwise be expected because of their exposure to fine particulate matter. The NRDC report recommends that the EPA establish a $PM_{2.5}$ standard of 10 $\mu g/m^3$ on an annual average basis and stringent new limits on 24-hour concentrations.

Given the potential significance of a new $PM_{2.5}$ standard to the well-being of Michigan's citizens and economy, I am requesting that the Michigan Environmental Science Board (MESB) thoroughly evaluate the air quality and human health scientific assumptions, interpretations and conclusions contained in the NRDC report. The MESB evaluation should determine the following:

1. Identify and evaluate the validity of the key air quality and human health assumptions. This would necessarily entail a thorough review of previously published reports by Brigham Young and Harvard Universities, the EPA and the CACAC.

2. Identify and evaluate the appropriateness of the methodology used to develop NRDC estimates of mortality and determine if there was sufficient evidence to attribute causality.

I would encourage the MESB to seek assistance in this assignment from appropriate state and federal agencies, your peers in the academic and scientific communities and the Natural Resources Commission's Air Quality Relative Risk Task Force. I would appreciate receiving your report as soon as possible.

Thank you for your continuing service to the State of Michigan.

Sincerely,

John Engler
Governor

JE/rlf/pw

cc: Mr. Russell J. Harding, Director, MDEQ
Mr. James K. Haveman, Director, MDCH
Mr. Keith Harrison, Executive Director, MESB
Mr. George Wolff, Chair, AQRRTF

December 4, 1996

Dr. Lawrence Fischer, Chair
Michigan Environmental Science Board
Lewis Cass Building, 2nd Floor
P.O. Box 30026
Lansing, Michigan 48909

Dear Dr. Fischer:

As you know, the U.S. Environmental Protection Agency (EPA) has now released its proposed revisions to the National Ambient Air Quality Standards. On November 21, I asked you to evaluate a Natural Resources Defense Council report concerning the human health impact of ground-level ozone and particulate matter. As part of that assignment, I also asked you to conduct a thorough review of previously published studies on this issue. EPA has based their proposed revisions to the particulate matter and ozone standard on these studies, in one instance stating that the revised standards will "reduce premature deaths by 40,000 per year." I, too, am concerned about any potential human health effects of air quality. Thus, I would reiterate and expand my request to the Michigan Environmental Science Board by asking that you thoroughly review the human health assumptions, interpretations and conclusions of the studies that are the basis of EPA's proposed rules.

Given the short review and public comment period on EPA's proposed rules, I would appreciate receiving your report as soon as possible. Thank you, once again, for your continuing service to the State of Michigan.

Sincerely,

John Engler
Governor

JE/rlf/pw

cc: James K. Haveman, Director, MDCH
Russel J, Harding, Director, MDEQ
Keith G. Harrison, MESB
George Wolff, Chair, AQRRTF

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APPENDIX 2

Epidemiological Mortality and Morbidity Studies Summary Tables

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Table 1. Review of epidemiological mortality cohort studies.

Author	Study Date	Location of Study Subjects	Exposure Assessment (size of particulate)	Statistical Model	Strength of Association: Rate Ratio	Strength of Association: Particulate change for increased risk	Confounders Accounted For
Abbey[1]	1977-1986	California	TSP (*)	Cox proportional-hazards regression models	RR=0.99	1000 hrs @ >2000μg/m^3	Age, sex, education, smoking, obstructive respiratory symptoms
Dockery[2]	1974-1991	Six Cities	$PM_{2.5}$ (**)	Cox proportional-hazards regression models	RR=1.26	18.6μg/m^3	Age, sex, cigarette smoking, education level, body-mass index, occupational exposure, diabetes, hypertension
Pope[3] **(ACS)**	1982-1989	U.S. (50 areas)	$PM_{2.5}$ (***)	Cox proportional-hazards regression model	RR=1.17	24.5μg/m^3	Temperature, cigarette smoke, education level, occupational exposure, alcohol use, body mass, age, gender, race

(1) Abbey: This study measured total suspended particulates (TSP). *Cumulative ambient concentrations of particulate air pollutants were estimated by interpolating monthly statistics from air monitoring stations statewide to ZIP codes of residence and work location. Age- and sex-adjusted relative risks were calculated for each level of the pollutant using an adaptation of the Mantel-Haenszel method for person-years data. Further evaluations of this study focused on morbidity rather than mortality. **[Abbey *et al.*, 1991]**

(2) Dockery: This study measured particles with an aerodynamic diameter equal to or less than 2.5 μm ($PM_{2.5}$). **Mean pollution levels were calculated for each city and city mortality rate ratios were compared. The adjusted mortality ratio is 1.26 when comparing the most polluted to the least polluted city. The difference in level of $PM_{2.5}$ was 18.6 μg/m^3. The six cities included: Watertown, Massachusetts; Harriman, Tennessee; St. Louis, Missouri; Steubenville, Ohio; Portage, Wisconsin; and Topeka, Kansas. **[Dockery *et al.*, 1993]**

(3) Pope: American Cancer Society (ACS) study. ***Mean air pollution levels were determined for the years of 1979 to 1983. Although the risk is small compared with smoking, increased mortality is associated with sulfate and fine particulate air pollution at levels commonly found in U.S. cities. **[Pope *et al.*, 1995]**

Table 2. Review of positive epidemiological time-series mortality studies.

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size and lag time to mortality seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Anderson[1]	1987-1992	London, England	Black smoke (0-3 days) particles	Log-linear regression	RR=1.017	14μg/m^3	Season, day of week, temperature, relative humidity, influenza epidemic
Archer[2]	1970-1986	Utah	TSP (annual avg.)	Direct age adjustment	30-40% incr. mortality	23μg/m^3	Cigarette smoking, age, occupation, indoor pollution sources
Ballester[3]	1991-1993	Valencia, Spain	Black smoke (0 days)	Poisson regression	RR=1.008-1.1.012	10μg/m^3	Not specified
Bobak[4]	1986-1988	Czech Republic	TSP-10 (annual avg.)	Logistic regression	RR=2.41	31.1μg/m^3	Socioeconomic factors, SO_2, nitrogen oxides
Borja-Aburto [5]	1990-1992	Mexico City, Mexico	TSP (0 days)	Poisson regression	RR=1.058-1.095	100μg/m^3	Season, temperature, day of week, ozone, SO_2
Buechley[6]	1962-1966	New York-New Jersey	SO_2 (0 days) coefficient of haze (COH)	Multiple regression	Steady progression upward of mortality		Season, heat waves, influenza epidemics, warm and cold weather, day of week, holidays
Buffler[7]	1979-1981	Harris County, Texas	TSP (0-7 days)	Linear multiple regression analysis	<5% of excess urban lung cancer mortality		Age, smoking habits, socioeconomic status
Davis[8]	1985-1988	Birmingham, Alabama	PM_{10} (0-2 days)	Linear regression	RR=1.04	100μg/m^3	Relative humidity, season, temperature
Dockery[9]	9/85-8/86 Missouri	St. Louis	PM_{10} (1 day)	Poisson process time series analysis	RR=1.16	100μg/m^3	Weather variables/seasonal Indicators, temperature, humidity
Fairley[10]	1980-1986	Santa Clara County, CA	COH (0-2 days)	Regression analysis	+0.0084 daily deaths/COH unit		Temperature, humidity

Table Notes follow last page of Table 2.

Table 2. Review of positive epidemiological time-series mortality studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size and lag time to mortality seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Glasser[11]	1960-1964	New York City, New York	SO_2 (0 days) and smoke shade	Regression analyses, descriptive statistics, cross tabulations	+15 deaths	.20ppm SO_2	Weather, season, temperature
Greenburg[12]	01/63-02/63	New York City, New York	SO_2 (weekly avg.) and smoke shade	Poisson distribution	Increase in mortality ages >44, all causes		Influenza virus activity
Hickey[13]	1962	26 U.S. cities	Particulates and certain elements (year average)	Multivariate statistical analysis	Metals more significant than particulates		None specified
Ilto[14]	1965-1972	London, England	SO_2 (0-1 day) British smoke and acidity	Regression models, cross-correlation function analysis	Significant association		Weather, temperature, humidity
Kinney[15]	1970-1979	Los Angeles, California	KM/B. ext	Linear regression	(See notes)		Temperature, humidity, day of week
Knöbel[16]	1981-1991	Taiwan	Visibility (0-9 days)	Poisson regression	RR=3.3-3.4 lowest category visibility compared to highest		Population size, weather, urbanization, infections
Lebowitz[17]	1962-1965	New York City, Los Angeles, Philadelphia	TSP (0-3 days) and weather	multiple regression stimulus-response method	Mortality is related to pollution and weather		Season, temperature, relative humidity
Mazumdar[18]	1958-1972	London, England	SO_2 (0 days) and British smoke	Multiple regression	1.165% increase mortality/mg/m^3 SO_2 25.09% increase mortality/mg/m^3 Smoke		Season, temperature, humidity, day of week
McCarroll[19]	1962-1964	New York City, New York	SO_2 (0 days) and smoke shade	Daily graphs of mortality & air pollution	Mortality peaks coincide with pollution peaks		Natural disasters, infectious epidemics, age, atmospheric inversion, weather extremes
Ostro[20]	1989-1991	Santiago, Chile	PM_{10} (0-2 days)	Poisson regression	RR= 1.06-1.15	10μg/m^3	Temperature extremes, season, month, day of week

Table Notes follow last page of Table 2.

Table 2. Review of positive epidemiological time-series mortality studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to mortality seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Ostro[21]	1992-1995	Bangkok, Thailand	PM_{10} (0-2 days)	Poisson regression multivariate	Increased mortality 1.5 to 5.0%	10μg/m^3	Temperature, humidity, season, day of week, time
Penna[22]	1980	Rio de Janeiro, Brazil	Particulates (annual level)	Linear regression	Significant association		Area of residence, income
Pope[23]	04/85-12/89	Utah Valley, Utah	PM_{10} (0-4 days)	Poisson regression	RR=1.076	50μg/m^3	Temperature, humidity, season
Saldiva[24]	05/90-04/91	Sao Paulo, Brazil	PM_{10} (0-2 days)	Poisson regression	RR=1.13	100μg/m^3	Month, temperature, relative humidity, season
Schwartz [25]	1958-1972	London, England	Particulates (0 days)	Multiple regressions	Coefficient of +2.31		Temperature, humidity, year
Schwartz[26]	1977-1982	Cincinnati, Ohio	TSP (0 days)	Poisson regression	RR=1.06-1.18	100μg/m^3	Temperature, relative humidity, seasonal and monthly variations
Schwartz[27]	1973-1980	Philadelphia, Pennsylvania	TSP (0-1 day)	Poisson regression	7% increase total mortality	100μg/m^3	Year, season, temperature, humidity
Schwartz[28]	1973-1982	Detroit, Michigan	TSP (0-1 day)	Poisson regression	RR=1.06	100μg/m^3	Weather, temperature, humidity
Schwartz[29]	1974-1984	Steubenville, Ohio	TSP (1 day)	Poisson regression	RR=1.04	100μg/m^3	Season, temperature
Schwartz[30]	1985-1988	Birmingham, Alabama	PM_{10} (0-4 days)	Poisson regression	RR=1.11	100μg/m^3	Weather, day of week, season, time trends
Shumway[31]	1970-1979	Los Angeles, California	KM (0 days) CO, hydrocarbons	Linear regression	Increased mortality (predicted)		Temperature, relative humidity
Tango[32]	1972-1988	Tokyo, Japan	SO_2/NO_2 (mean daily levels)	Poisson regression	Long-term effects on lung cancer seen		Not specified

Table Notes follow last page of Table 2.

Table 2. Review of positive epidemiological time-series mortality studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to mortality seen)	Statistical Model	Strength of Association OR/RR Particulate change for increased risk	Confounders Accounted For
Vigotti[33]	1980-1989	Milan, Italy	TSP (0 days) SO_2	Time series analysis	Increased risk of respiratory death	Not specified
Wichmann[34]	01/85-02/85	Germany	Suspended particulates (0-1 day)	Regression analysis	Increased mortality	Temperature, humidity
Wietlisbach[35]	1984-1989	Switzerland	TSP (0-3 days)	Various regressions	Increased mortality	Time trends, seasonal factors, weather variables
Xu[36]	1989	Beijing, China	TSP (0 days)	Poisson regression	4% increased mortality with doubling of TSP	Temperature, humidity, season

Table 2 Notes:

(1) Anderson: In the Zeger approach, the daily number of deaths was used as the outcome variable in auto-regressive log-linear regression models with Poisson errors implemented. **[Anderson *et al.*, 1996]**

(2) Archer: Utah and Cache Counties were similar until the construction of a steel mill in Utah County during World War II. Operation of this mill caused a substantial rise there in pollution. Salt Lake County was included in this study for comparison as a representative of counties outside Utah. The excess respiratory cancer and nonmalignant respiratory disease mortality in Utah County, in the absence of other significant differences, is evidence of a large component (i.e., 30% - 40%) being attributable to community air pollution. **[Archer, 1990]**

(3) Ballester: **[Ballester *et al.*, 1996]**

(4) Bobak: **[Bobak and Leon, 1992]**

(5) Borja-Aburto: TSP was recorded every sixth day as a 24-hour integrated measure. The analysis was based on the subset of days when TSP measurement was available. TSP measurements for central Mexico were highly correlated with same day PM_{10} measurements. PM_{10} TSP ratio equalled approx. 0.50 (correlation coefficient 0.82). RR equalled 1.058 for total mortality. RR equalled 1.095 for respiratory mortality. Both were based on changes in airborne TSP of 100 $\mu g/m^3$. **[Borja-Aburto *et al.*, 1977]**

(6) Buechley: Partial predicted mortality values were computed from regression weights of the full regression equation, except for that of SO_2, and subtracted from the observed values to get partial residual mortality values. This relationship between SO_2 and mortality has a significant r value of 0.1444. There is a steady upward progression of mean mortality residuals as SO_2 values rise. **[Buechley *et al.*, 1973]**

Table 2 Notes (continued):

(7) Buffler: With the onset of high levels of air pollution, daily deaths due to all causes immediately rose to higher than expected levels and remained at higher than expected levels for seven consecutive days. There were 24 more deaths per day than during the control periods for a total of 168 excess deaths. It was difficult to separate the effects of air pollution from those of smoking, occupation, and social status which may be more important predictors of mortality. **[Buffler *et al.*, 1987]**

(8) Davis: The authors re-examined the effect of atmospheric particles on human mortality in Birmingham using the same initial data as Schwartz, but with alternative models. The particles measured were those with an aerodynamic diameter equal to or less than 10 μm (PM_{10}). In the initial analysis, normal linear regression is employed together with a square root transformation. [**Davis *et al.*, 1996]**

(9) Dockery: Poisson model: log(E(Y)) = XB, where E(Y) = expected value of daily deaths Y, X = matrix of covariates, B = vector of estimated regression coefficients. Estimated percentage increase in deaths attributed to air pollution based on this model is given by $(e^{\beta x}-1)100$ where x is the mean pollution concentration and β is the regression coefficient for the pollutant. **[Dockery, Schwartz and Spengler, 1992]**

(10) Fairley: The predicted increase of 0.0084 daily deaths in Santa Clara per coefficient of haze (COH) unit gives a coefficient which is at least as large as those of the London studies. Particulates may be a health risk at concentrations lower than previously suspected. Further study is needed to identify the specific constituents within the particle mix which are causing the health problems. **[Fairley, 1990]**

(11) Glasser: Smoke shade is a measure of suspended particulate matter. Smoke shade is related to mortality since SO_2 and smoke shade are correlated positively and SO_2 is correlated positively with mortality. **[Glasser and Greenburg, 1971]**

(12) Greenburg: In New York City, the months of January and February of 1963 were among the coldest in decades resulting in both cold stress and increased fuel consumption which would have contributed to the excess pollution. During the control periods, influenza and cold weather were present but air pollution was not. Estimates of the effect of air pollution ranged from approximately 200 to 400 excess deaths. Controls included: (1) days prior and subsequent to the episode, (2) a similar period of 15 days during 1958, and (3) days prior to and subsequent to the period in 1958. **[Greenburg *et al.*, 1967]**

(13) Hickey: The rank order of importance of the air pollutants examined as predictors of heart disease mortality is cadmium followed by vanadium. More extensive input data on general environmental pollutants should be obtained from other communities or rural areas. **[Hickey Schoff and Clelland, 1967]**

(14) Ito: All pollutants measured daily were found to be associated significantly with mortality effects. It is not appropriate, however, to interpret the small differences in strength of association among the three pollutants considered as indicative of their respective importance to mortality. This is because of the pollutants' collinearity and the lack of quantitative information on their relative measurement errors. Mean pollution effects with full temperature and humidity controls ranged from 2.4 percent to 3.3 percent excess deaths. **[Ito *et al.*, 1993]**

(15) Kinney: KM is a measure of particulate optical reflectance. B.ext is the extinction coefficient which was derived from noontime visual range measurements by the Koschmeider formula, with relative humidity correction. B.ext was an alternative to KM as an estimate of fine particulate matter concentrations. The authors demonstrated associations between short-term variations in total mortality (excluding accidents and suicides) and pollution, controlling for temperature. Multiple linear regression models were fit with mortality as the outcome variable and up to eight environmental variables were used as regressors. A parsimonious three variable model (NO_2, 1-day lagged O_x, and temperature) explained four percent of the short-term variation in total mortality. NO_2, CO, and/or KM were difficult to separate due to their high correlation. **[Kinney and Özkaynak, 1991]**

(16) Knöbel: **[Knöbel, Chen and Liang, 1995]**

Table 2 Notes (continued):

(17) Lebowitz: Environmental events are defined as blocks of adjoining days of abnormal pollution, temperature, or humidity. These are called stimuli. Responses are defined as blocks of adjoining days of excess mortality. Response was associated with a given stimulus if it started within the time period of the stimulus until one to three days after the end of the stimulus. Association of stimulus days with response was 50 percent - 72 percent. Association of response days with stimulus was 52 percent - 77 percent. **[Lebowitz, 1973]**

(18) Mazumdar: A large data base and three different methods of analysis gave the conclusion that the pollution/mortality association was due almost entirely to smoke (analyses: (1) separate multiple regressions for each winter, (2) stratification with two-way nested quartiles, and (3) multiple regression of high pollution data). **[Mazumdar, Schimmel and Higgins, 1982]**

(19) McCarroll: Examination of total deaths in New York City (during five separate episodes) by day of occurrence showed periodic peaks in mortality which are associated with periods of high air pollution (usually periods of low wind speed and temperature inversion). Principal effect on mortality was on the first day and the increase was noted in all age groups above 45 years. **[McCarroll and Bradley, 1966]**

(20) Ostro: Daily monitoring was done at five sites in Santiago. During the three-year period the mean of the 24-hour average of PM_{10} was 115.4 $\mu g/m^3$. A 10 $\mu g/m^3$ change in PM_{10} was seen to be associated with a one percent change in mortality. RR equalled 1.06 for total female mortality. RR equalled 1.15 for respiratory mortality-male and female. Ordinary least squares regression techniques and parametric tests were used in examining the association between air pollution and total mortality. **[Ostro *et al.*, 1995]**

(21) Ostro: [**Ostro et al 1997]**

(22) Penna: **[Penna and Duchiade, 1991]**

(23) Pope: The authors were able to assess risk after elimination of the main pollution source -- closure of the steel mill. **[Pope, Schwartz and Ransom, 1992]**

(24) Saldiva: Pairwise Pearson correlation coefficients for daily values of deaths, pollution concentrations, low temperatures and relative humidity were calculated. Multiple regression models estimated the association between daily mortality and air pollution, controlling for month, temperature, humidity and day of week. **[Saldiva *et al.*, 1995]**

(25) Schwartz: **[Schwartz and Murawski, 1976]**

(26) Schwartz: **[Schwartz and Marcus, 1990]**

(27) Schwartz: Generalized additive model, which models the expected number of deaths as a nonparametric smoothed function of the covariates, was used to ensure adequate control for any nonlinearities in the weather dependence. No evidence of threshold was seen down to the lowest observed exposure levels. **[Schwartz and Dockery, 1992a]**

(28) Schwartz: **[Schwartz, 1991]**

(29) Schwartz: **[Schwartz and Dockery, 1992b]**

(30) Schwartz: **[Schwartz, 1993]**

Table 2 Notes (continued):

(31) Shumway: KM monitors draw ambient air through a segment of porous tape during two-hour intervals and then measure the amount of light transmitted through the tape. This measures the particulates thought to be small enough to penetrate deep into the human lung. Linear and nonlinear models investigate possible associations between mortality, pollution and weather. Significant weather factors and pollutants were isolated. Parametric nonlinear time series model with linear & squared terms in temperature and the logarithm of pollution provides a reasonable predictive model. At 72°F predicted daily deaths increased from about 160 at a KM level of 20 to about 172 at a Km level of 80 for a dynamic range of about 12 deaths. At a KM level of 52, the 168 deaths/day at 72°F would increase to 184 deaths/day at 98°F for a dynamic range of about 16 deaths per day. **[Shumway, Azari and Pawitan, 1988]**

(32) Tango: **[Tango, 1994]**

(33) Vigotti: **[Vigotti *et al.*, 1996]**

(34) Wichmann: If the one-week period of the smog episode is compared with the period of observation (which also includes the two weeks before and after the episode) one finds a significant increase in the number of deaths per day by eight percent in the polluted area but only by two percent in the control area. It cannot be excluded that at the end of the smog period, because of the change of weather, synergistic influences of meteorology and pollutants occurred. However, the general meteorological situation was the same in the polluted area and in the control area. **[Wichmann *et al.*, 1989]**

(35) Wietlisbach: **[Wietlisbach, Pope and Ackermann-Liebrich, 1996]**

(36) Xu: **[Xu *et al.*, 1994]**

Table 3. Review of inconclusive epidemiological time-series mortality studies.

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to mortality seen)	Statistical Model	Strength of Association OR/RR Particulate change for increased risk	Confounders Accounted For
Bacharova (1)	1987-1991	Bratislava, Slovak Republic	SO_2/TSP (0 days)	Poisson regression	RR=1.008	Season, temperature, relative humidity, holidays, secular trends, day of week
Hagstrom(2)	1949-1960	Nashville, Tennessee	Suspended particulates averages for study period	Adjusted death rates by degree of exposure	Inconclusive, varied by cancer site & pollutant	Age, race, sex
Hatzakis(3)	1975-1982	Athens, Greece	SO_2 (0 days) smoke	Multiple regression	Mortality: SO_2 concentration regression coefficient = +0.0058	Season, temperature, humidity, holidays, day of week
Krzyzanowski(4)	1977-1989	Cracow, Poland	PM_{20} (0-4 days) SO_2	Pearson correlations	Correlation coefficient = 0.093 (0.141 for SO_2)	Age, sex, month, day of week
Li(5)	1973-1990	Philadelphia, PA Birmingham, AL Toronto, Canada	PM_{10} (0-2 days) TSP	Poisson regression log and square root	Mixed results	Temperature, humidity, barometric pressure, precipitation, other pollutants
Styer(6)	1985-1990	S. L. County, UT Cook County, IL	PM_{10} (0-2 days)	Poisson regression	No effects seen-UT Seasonal effects-IL	Weather

Table 3 Notes:

(1) Bacharova: **[Bacharova *et al.*, 1996]**

(2) Hagstrom: During 1958 - 1959 Nashville had an average annual geometric mean of suspended particulate matter of 125 $\mu g/m^3$. Death rates for "all cancer" were higher (P = 0.05) in the area of high pollution compared to moderate pollution for only one pollutant, suspended particulates as measured by the soiling index (additional studies needed to control factors such as smoking, occupation, and class). Suspended particulates and dustfall are composed of many pollutants, and levels of both these and SO_2 may rise or fall concomitantly with other pollutants which were not, or were not able to be, measured. **[Hagstrom, Sprague and Landau, 1967]**

(3) Hatzakis: The dependent variable was the difference between the observed total mortality and the expected mortality predicted on the basis of a sinusoid curve fitted to the monthly mortality data for the years 1956 - 1958 in the Athens area. There was no significant or consistent association between smoke and mortality when the other independent variables were taken into account. There was a positive and statistically significant association of excess mortality with SO_2 concentration; regression coefficient of +0.0058. **[Hatzakis *et al.*, 1986]**

Table 3 Notes (continued):

(4) Krzyzanowski: **[Krzyzanowski and Wojtyniak, 1991/92]**

(5) Li: Mixed results occurred in Philadelphia and Birmingham for PM_{10}. Negative results occurred in Toronto for TSP. **[Li and Roth, 1995]**

(6) Styer Weather was seen to have an effect on both mortality and particulate levels. The semi-parametric model suggests an isolated PM_{10} effect limited to the month of June in Utah. There was a significant effect seen during the spring and fall in Cook County, Illinois. **[Styer *et al.*, 1995]**

Table 4. Review of epidemiological morbidity studies.

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to health effects seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Abbey[1]	1973-1987	California	PM_{10} (yearly avg.)	Logistic regression	RR=1.17 -1.30	1,000 h/yr >100µg/m^3	Occupational exposure, race, age, religion
Abbey[2]	1977-1986	California	$PM_{2.5}$ (*)	Multiple regression	RR=1.46	45µg/m^3	Sex, age, education, exposure to passive smoke
Ackermann-Liebrich[3]	1991	Switzerland	PM_{10} (annual means)	Logistic regression	3.4%dec FVC	10µg/m^3	Smoking, respiratory infections, age, sex, height occupational exposure, education
Anderson[4]	1991	London, England	Black smoke (week avg.)	Log linear modeling	RR=1.22	105µg/m^3	Weather, respiratory viruses, publicity
Brabin[5]	12/90-11/91	Merseyside, England	Coal dust (year avg.)	Logistic regression	OR=1.55	40mg/m^3	Allergies, sex, economic status
Braun-Fahrlander[6]	11/85-11/86	Switzerland	TSP (six-week avg.)	Poisson Regression -a priori judgment	RR=1.12-1.16	20µg/m^3	Previous illness, weather, daily mean temp & humidity
Braun-Fahrlander[7]	1992-1993	Switzerland	PM_{10} (annual means)	Logistic regression	OR=2.17-3.07	23µg/m^3	Prior respiratory symptoms
Burnett[8]	1983-1988	Ontario, Canada	Sulfate (0-1 day) particulates	Linear regression	2.8-3.7% inc. admissions	13µg/m^3	Seasonal patterns, temperature, ozone,
Delfino[9]	1992-1993	Montreal, Canada	PM_{10} (0-1 day) $PM_{2.5}$	Regression models Pearson correlation	0.2-0.26 ER visits/µg/m^3		Temporal trends, autocorrelation, weather
Gordian [10]	05/92-03/94	Anchorage, Alaska	PM_{10} (0 days)	Data filtered	1-6% inc. visits	10µg/m^3	Seasonal trends, temperature, day of week
Hoek[11]	1987-1991	Netherlands	PM_{10} (0-1 day)	Box-Jenkins	No association **		Minimum temperatures, chronic respiratory symptoms
Lipsett[12]	1986-1992	N. California	PM_{10} (2 days)	Poisson regression	RR=1.11-1.43	60µg/m^3	Season, time trends, temperature

Table Notes follow last page of Table 4.

Table 4. Review of epidemiological morbidity studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time) to health effects seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Neas [13]	06/90-08/90	Uniontown, Pennsylvania	PM_{10} (0 days)	Linear regression	dec. PEFR	20μg/m^3	Temperature, time of day, precipitation
Ostro[14]	1978-1979	S. California	Sulfate particulates-(measured every 6th day)	Mult. logistic regression	OR=1.30 mean SO_3 8.43μg/m^3 conc.	10μg/m^3	Temperature, day of week (weekends)
Ostro[15]	1987-1988	Denver, Colorado	H+ (0 days) $PM_{2.5}$ (0 days)	Multiple regression (time-series model)	Inc. cough and shortness of breath		Geography, ozone
Pantazopoulou[16]	1988	Athens, Greece	Black smoke (0 days)	Linear regression	15-29%inc ER visits	235μg/m^3	Season, weather
Peters[17]	09/90-06/92	Eastern Europe	PM_{10} (0-5 days)	Linear regression	-0.43%PEF	54μg/m^3	Time trends, temperature, relative humidity
Peters[18]	1991-1992	Erfurt, Germany	PM_{10} (0-5 days) $PM_{2.5}$	Regression models Pearson correlation	OR=1.2-1.32	51μg/m^3	Temperature, day of week, viral infections
Pönkä[19]	1987-1989	Helsinki Finland	TSP (0 days)	Poisson regression	No observed association		Age, temperature, relative humidity
Pope[20]	04/85-03/89	Utah, Salt Lake, & Cache Valleys	PM_{10} (monthly mean-lagged)	Regression analysis	OR=1.14-2.09	~50μg/m^3	Temperature, smoking rates
Pope[21]	01/87-01/89	Salt Lake City, Utah	PM_{10} (***)	Regression models	2%dec FEV	100μg/m^3	Temperature
Pope[22]	12/89-03/90	Utah Valley, Utah	PM_{10} (0-2 days)	Weighted least squares regression models	OR=1.06	41μg/m^3	Temperature
Ransom[23]	1985-1990	Utah Valley, Utah	PM_{10} (0-28 days)	Regression models	40% increase overall absences	100μg/m^3	Temperature, snowfall, day of week, month of school year, holidays, weekends
Romieu[24]	05/91-02/92	Mexico City, Mexico	PM_{10} (0-2 days) $PM_{2.5}$ (0-2 days)	Linear regression	OR=1.08 OR=1.08-1.19	20μg/m^3 10μg/m^3	Temperature

Table 4. Review of epidemiological morbidity studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to health effects seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Scarlett[25]	06/94-07/94	Surrey, England	PM_{10} (0-1 day)	Autoregressive models (weighted slope average)	1% dec FVC	130μg/m^3	Pollen levels, temperature, time trends
Schwartz[26]	1986-1989	Birmingham, Alabama	PM_{10} (0 days)	Poisson regression	RR=1.19-1.27	100μg/m^3	Time trends, season, weather, temperature, dew point
Schwartz[27]	1988-1990	Cleveland, Ohio	PM_{10} (0-2 days)	Poisson regression	RR=1.12	100μg/m^3	Season, weather, day of week
Schwartz[28]	1986-1989	Detroit, Michigan	PM_{10} (0 days)	Poisson regression	RR=1.02	32μg/m^3	Season, temperature, dew point
Schwartz[29]	1986-1989	Detroit, Michigan	PM_{10} (0 days)	Poisson regression	RR=1.012	10μg/m^3	Seasonal & long-term temporal trends, temperature, dew point temperature
Schwartz[30]	1986-1989	Minneapolis-St. Paul, Minnesota	PM_{10} (0 days)	Poisson regression	RR=1.17-1.57	100μg/m^3	Time trends, seasonal fluctuations, weather
Schwartz[31]	09/89-09/90	Seattle, Washington	PM_{10} (0-4 days)	Poisson regression	RR=1.12	30μg/m^3	Weather, season, time trends, age, hospital, day of week
Schwartz[32]	01/88-12/90	New Haven, Connecticut, Tacoma, Washington	PM_{10} (0 days)	Poisson regression	RR=1.06 RR=1.10	50μg/m^3	Temperature, humidity, other pollutants
Schwartz[33]	<1996>	Spokane, Washington	PM_{10} (0 days)	Poisson regression	RR=1.085	50μg/m^3	Temperature, humidity
Studnicka[34]	06/91-08/91	Austria	H+/PM_{10} (0-4 days)	Linear regression	-2.99 ml FEV_1/nmolm^3 H+		Sex, age, height, temperature, humidity
Sunyer[35]	1985-1986	Barcelona, Spain	SO_2 (0-2 days) black smoke	Autoregressive and average linear regression	OR=1.06-1.09	25μg/m^3	Season, weather, day of week

Table 4. Review of epidemiological morbidity studies (continued).

Author	Study Date	Location of Study Subjects	Exposure Assessment (particle size & lag time to health effects seen)	Statistical Model	Strength of Association OR/RR	Particulate change for increased risk	Confounders Accounted For
Vedal[36]	1979-1981	Chestnut Ridge, Pennsylvania	COH (0 days)	Regression analysis	No air pollutant was strongly associated with respiratory disease		Temperature, previous symptoms
Vigotti[37]	1980-1989	Milan, Italy	TSP (0 days)	Poisson regression	RR=1.05	100μg/m^3	Weather, season, day of week, influenza epidemic
Xu[38]	1990	Beijing, China	TSP (0 days)	Linear regression	17% inc. visits	1149μg/m^3	Temperature, humidity, season, day of week

Table 4 Notes:

(1) Abbey: The authors measured the development of respiratory symptoms in a non-smoking population associated with changes in PM_{10} concentrations. RR equalled 1.17 for development of airway obstructive disease in those exposed to 1,000 hours per year of PM_{10} at concentrations of over 100 μg/m^3. RR equalled 1.21 for development of productive cough, and RR equalled 1.30 for development of asthma. Stronger associations were observed for those who were exposed occupationally to dust and fumes. **[Abbey *et al.*, 1995a]**

(2) Abbey: The authors measured development of new respiratory symptoms: airway obstructive disease (AOD), chronic bronchitis and asthma in those individuals who did not have definite symptoms in 1977. *Cumulative ambient concentrations of fine particulates ($PM_{2.5}$) were estimated from airport visibility data. Site/season-specific regression equations were formed from 1,767 paired $PM_{2.5}$/visibility observations available between 1979 and 1986 and applied to visibility data at nine airports throughout California to estimate $PM_{2.5}$ concentrations in the vicinity of these airports for the years 1966-1986. **[Abbey *et al.*, 1991]**

(3) Ackermann-Liebrich: The effect of long-term exposure to air pollutants was measured using a cross-section of three plus year residents of eight different Swiss communities. Significant and consistent effects on forced vital capacity (FVC) and forced expiratory volume (FEV_1) were found for NO_2, SO_2, and PM_{10} with PM_{10} showing the most consistent effect. Atopy did not influence this relationship. **[Ackermann-Liebrich *et al.*, 1997]**

(4) Anderson: The authors measured the increase in respiratory disease and hospital admissions during an air pollution episode in London in December 1991. The air pollution episode was associated with an increase in morbidity unlikely to be explained by prevailing weather, a coincidental respiratory epidemic or psychological factors due to publicity. Relative roles of NO_2 and particulates cannot be distinguished. **[Anderson *et al.*, 1995]**

(5) Brabin: A cross sectional study was carried out to determine whether schoolchildren in a specific locality exposed to pollution from steam coal dust have an excess of respiratory symptoms compared with children in control areas. The exposed zone was confirmed as a significant risk factor for absenteeism from school due to respiratory symptoms (OR = 1.55). **[Brabin *et al.*, 1994]**

Table 4 Notes (continued):

(6) Braun-Fahrlander: TSP was a significant predictor of duration of respiratory symptoms. Incidents were modeled using Poisson regression: lnE(Yi)=XiB +lnNi (maximum likelihood estimation used), where Yi equals number of incidents, Xi equals risk factors for the ith child, Ni equals number of non missing days for child, and E equals expected value. The regression model used "a priori" judgment to determine covariates. RR equalled 1.12 for the duration of any respiratory episode with a 20 $\mu g/m^3$ change in exposure; RR equalled 1.16 for coughing incidences; and RR equalled 1.19 for upper respiratory symptoms. **[Braun-Fahrlander *et al.*, 1992]**

(7) Braun-Fahrlander: Impact of long-term exposure to air pollution on respiratory and allergic symptoms and illnesses was assessed in a cross-sectional study of schoolchildren living in ten different communities in Switzerland. For PM_{10}, NO_2, SO_2, and O_3 the strongest relationship was observed for PM_{10}. Adjusted odds ratios for chronic cough, nocturnal dry cough, and bronchitis between the most and least polluted community for PM_{10} were 3.07, 2.88, and 2.17, respectively. There was some indication that frequency of fog is a risk factor for chronic cough and bronchitis, independent of air pollution. [**Braun-Fahrlander *et al.*, 1997]**

(8) Burnett: The authors measured the association between daily admissions for cardiac and respiratory illnesses and daily particulate sulfate levels in ambient air. A 13 $\mu g/m^3$ increase in sulfates on the day prior to admission was associated with a 3.7 percent increase in respiratory admissions and a 2.8 percent increase for cardiac admissions. **[Burnett *et al.*, 1995]**

(9) Delfino: An increase to the mean level of one-hour maximum O_3 (36 ppb) was associated with a 21 percent increase over the mean number of daily emergency room (ER) visits. Effects of particulates were smaller, with mean increases of 16 percent, 12 percent and 6 percent for PM_{10}, $PM_{2.5}$, and SO4, respectively. Ozone and PM_{10} levels never exceeded 67 ppb and 51 $\mu g/m^3$, respectively. **[Delfino *et al.*, 1997]**

(10) Gordian: **[Gordian *et al.*, 1996]**

(11) Hoek: The authors measured the association of the incidence of acute respiratory symptoms and air pollution concentrations on the same and previous day. **Mean PM_{10} concentration was 44.9 $\mu g/m^3$. Box-Jenkins: logistic regression model with prevalence or incidence as the dependent variable, one pollutant concentration as the independent variable and a first-order autoregressive parameter to describe the autocorrelation in the residuals. **[Hoek and Brunekreef, 1994]**

(12) Lipsett: **[Lipsett, Hurley and Ostro, 1997]**

(13) Neas: Personal exposure was modeled by weighting central site concentrations by proportion of time spent outdoors during the prior 12 hours. Mean deviation in peak expiratory flow rate (PEFR) was analyzed by an autoregressive linear regression model. Increments of 20 $\mu g/m^3$ in the 24-hour average concentration of PM_{10} was associated with a 1.23 liters/minutes change in the evening PEFR. **[Neas *et al.*, 1995]**

(14) Ostro: This study was primarily concerned with the effects of ozone on respiratory morbidity. Incidences of symptoms were used as dependent variables in multiple logistic regression. A pooled cross-sectional time series model was used for the presence or absence of an illness event. OR equalled 1.30 lower respiratory tract symptoms for a 10 $\mu g/m^3$ change. **[Ostro *et al.*, 1993]**

(15) Ostro: The authors investigated whether acidic aerosols and other air pollutants are associated with respiratory symptoms in free-living asthmatics. Airborne H+ was found to be significantly associated with several indicators of asthma status including moderate or severe cough and shortness of breath. Cough was also associated with fine particles, and shortness of breath with sulfates. Incorporating participants' time spent outside and exercise intensity into the daily measure of exposure strengthened the association between pollutants and symptoms. **[Ostro *et al.*, 1991]**

Table 4 Notes (continued):

(16) Pantazopoulou: The authors studied the short-term effects of air pollution on emergency room visits. The number of emergency admissions for cardiac and respiratory causes was related to a statistically significant degree with all indices of air pollution during the winter. There was a 15 percent - 17 percent increase in cardiac admissions and a 20 percent - 29 percent increase in respiratory admissions which were associated with an increase in pollution from the fifth to 95th percentile. **[Pantazopoulou *et al.*, 1995]**

(17) Peters: The authors assessed acute health effects of exposure to high levels of pollution in the Eastern European cities of Erfurt and Weimar, Germany and Sokolov, Czech Republic. A small decrease in pulmonary function and a small increase in reported symptom score associated with air pollution were observed in children with asthma. Effect estimates for the children were generally larger and more consistent than for the adults. **[Peters *et al.*, 1996]**

(18) Peters: OR equalled 1.20 for "feeling ill" during the day (same day). OR equalled 1.32 for cough (same day). Decreases in PEF and increased reporting of feeling ill during the day and of cough by adults with a history of asthma were associated with the number concentration and the mass concentration of the fine and ultrafine particles. Health effects of the five-day mean of the number of ultrafine particles were larger than those of the mass of the fine particles. This study suggests that the size distribution of ambient particles helps to elucidate the properties of ambient aerosols responsible for health effects. **[Peters *et al.*, 1997]**

(19) Pönkä: The authors measured the effect of ambient air pollution on asthma. Methodology was seen to have a strong effect on the results. Although results suggest that even low level pollution may increase hospital admissions for asthma, no definitive conclusion can be drawn without meta-analysis. **[Pönkä and Virtanen, 1996]**

(20) Pope: The author assessed the association between respiratory hospital admissions and PM_{10} pollution comparing periods when the main pollutant source was open and closed. Annualized admissions ratios during periods with the steel mill open to period with the mill closed showed ratios of 1.14 to 1.40 for respiratory admissions for all ages; ratios for preschool children were 1.24 to 2.09. Admissions were lower in Cache Valley (which had lower temperatures and higher smoking rates) than in Utah Valley which had higher rates of PM_{10}. **[Pope, 1991]**

(21) Pope: The authors measured the effect of acute exposure to respirable particulate pollution on the pulmonary function of current smokers. ***Spirometric data from two visits (10 to 90 days) apart were used to calculate change in pulmonary function and compared to pollution data for the same days. Individual deviations of daily performance from each participant's mean PEF's were calculated and averaged across participants to obtain a daily mean deviation. Weighted least-squares regression models were estimated using the inverse of the calculated SEM deviations (PEF values) as weights. Estimations were done using the Yule-Walker method. **[Pope and Kanner, 1993]**

(22) Pope: **[Pope *et al.*, 1991]**

(23) Ransom: The authors assessed the association between school absenteeism and respirable particulate pollution (PM_{10}) in Utah Valley for six school years. Similar relationships were observed for all grade levels although they were generally greater for first through third grades. Associations between absenteeism and PM_{10} pollution were observed even for levels below 150 $\mu g/m^3$. **[Ransom and Pope, 1992]**

(24) Romieu: The authors measured the relation between air pollution and the exacerbation of childhood asthma. OR for PM_{10} equalled 1.08 for respiratory symptoms with 1.06 for difficulty breathing and 1.10 for cough. OR for $PM_{2.5}$ equalled 1.08 for lower respiratory symptoms and 1.19 for coughing. **[Romieu *et al.*, 1996]**

Table 4 Notes (continued):

(25) Scarlett: The authors investigated the relationship between daily changes in ambient air pollution and short-term variations in respiratory function in children in the United Kingdom. They determined that there is a very small, but statistically significant, adverse effect of airborne respirable particulate matter, measured as PM_{10} on lung function. **[Scarlett *et al.*, 1996]**

(26) Schwartz: RR equalled 1.19 for pneumonia. RR equalled 1.27 for COPD. The author measured the association between PM_{10} and hospital admissions for respiratory disease. **[Schwartz, 1994]**

(27) Schwartz: The authors reviewed the issues and methodologies in time series studies of mortality and hospital admissions with an example from hospital admissions of the elderly in Cleveland. They concluded that adequate methods exist to control for weather and seasonality while examining the associations between air pollution and mortality and morbidity. **[Schwartz *et al.*, 1996]**

(28) Schwartz: The authors measured the association between PM_{10} and hospital admissions for cardiovascular disease. RR equalled 1.02 for ischemic heart disease. **[Schwartz and Morris, 1995]**

(29) Schwartz: The author measured the effects of PM_{10} (and ozone) on hospital admissions for asthma. Controlling for one pollutant did not affect the magnitude of the association with the other pollutant. **[Schwartz, 1994a]**

(30) Schwartz: The author measured the association between PM_{10} and ozone and hospital admissions for pneumonia and chronic obstructive pulmonary disease. RR equalled 1.17 for pneumonia admissions. RR equalled 1.57 for COPD admissions. **[Schwartz, 1994b]**

(31) Schwartz: The authors confirm whether PM_{10} exposure is a risk factor for the exacerbation of asthma by measuring hospital emergency room visits for asthma. **[Schwartz *et al.*, 1993]**

(32) Schwartz: The author found an association between short term changes in air pollution and respiratory hospital admissions in two cities with different levels of SO_2 but similar particulate levels. The PM_{10} associations were little changed by control for either ozone or SO_2. **[Schwartz, 1995]**

(33) Schwartz: The author measured the association between short-term changes in air pollution and respiratory hospital admissions in a location where SO_2 concentrations were found to be trivial. Magnitude of PM_{10} effect was similar to that reported in other locations in the eastern U.S. and Europe, where confounding by weather and SO_2 is a greater concern. **[Schwartz, 1996]**

(34) Studnicka: The authors measured the effects of acidic particles on lung function in children at an Austrian summer camp. They observed a decrease in FEV_1 of approximately 200ml for a two week acidic haze episode with maximal H+ of 84 nmol/m^3. They concluded that summer haze acidic particles may be associated with transient decreases in lung function in children. **[Studnicka *et al.*, 1995]**

(35) Sunyer: The authors measured the association between sulfur dioxide levels in urban air and the daily number of emergency room admissions for COPD. Relation between daily emergency room admissions and daily air pollution levels was determined by means of transfer function models (autoregressive and moving average linear regression models) which estimated by the maximum likelihood method, an adjusted coefficient for air pollution. A 25 $\mu g/m^3$ increase in sulfur dioxide produced an adjusted change of approximately 6 percent in the number of COPD emergencies during winter and 9 percent during summer. Particulate pollution in the form of black smoke showed a similar association in winter, but less of an association in summer. **[Sunyer *et al.*, 1993]**

Table 4 Notes (continued):

(36) Vedal: The authors sought to identify acute respiratory health effects on school-aged children associated with air pollution due to coal combustion. Respiratory illness on the preceding day was the most important predictor of current illness. The pollutant concentrations observed were uniformly lower than current ambient air quality standards, and exposure estimation was based on monitoring of ambient air which likely results in misclassification of the true exposure. **[Vedal *et al.*, 1987]**

(37) Vigotti: The authors investigated the association between daily urban air pollution and hospital admissions for respiratory causes. **[Vigotti *et al.*, 1996]**

(38) Xu: The authors measured the association of air pollution with hospital (non-surgery) outpatient visits. In a department-specific analysis, the association was found to be 1.5- to 2.0-fold stronger for pediatrics and internal medicine visits than for other types **[Xu *et al.,* 1995]**